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**ROYAL COMMISSION OF INQUIRY INTO CERTAIN  
DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND  
RELATED MATTERS.**

Hearing held in Court Room 20  
Court House  
361 University Avenue  
Toronto, Ontario

**The Honourable Mr. Justice S.G.M. Grange**

Commissioner

**P.S.A. Lamek, Q.C.**

Counsel

**E.A. Cronk**

Associate Counsel

**Thomas Millar**

Administrator

Transcript of evidence  
for

June 29th, 1983

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Court House, 361 University  
Avenue, Toronto, Ontario, on  
Wednesday the 29th day of June,  
1983.

THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner  
THOMAS MILLAR - Administrator  
MURRAY R. ELLIOTT - Registrar

APPEARANCES:

P.S.A. LAMEK, Q.C.)	Commission Counsel
E.A. CRONK )	
T.C. MARSHALL, Q.C.)	Counsel for the Attorney-
D. HUNT )	General and Solicitor
L. CECCHETTO )	General of Ontario (Crown
	Attorneys and Coroner's Office)
I.J. ROLAND )	Counsel for The Hospital for
R. DEVINS )	Sick Children
L. STERLING)	
D. YOUNG	Counsel for The Metropolitan
	Toronto Police
W.N. ORTVED	Counsel for numerous Doctors
	at The Hospital for Sick
	Children

(Cont'd)







APPEARANCES: (Continued)

B. SYMES ) Counsel for the Registered Nurses'  
F. KITELY ) Association of Ontario and 35  
Registered Nurses at The Hospital  
for Sick Children

W.A. BOGART)  
D.B. BROWN ) Counsel for Susan Nelles - Nurse

G.R. STRATHY)  
E. FORESTER ) Counsel for Phyllis Trayner - Nurse

M. ROSENBERG Counsel for Sui Scott - Nurse

N. GOODMAN Counsel for Mrs. Christie - R.N.A.

M. MANNING, Q.C.) Counsel for Mr. & Mrs. Gosselin,  
S. LABOW ) Mr. & Mrs. Gionas, Mr. & Mrs. Inwood,  
Mr. & Mrs. Turner, and Mr. & Mrs.  
Lutes (parents of deceased children)

F.J. SHANAHAN Counsel for Mr. & Mrs. Dominic  
Lombardo (parents of deceased child  
Stephanie Lombardo)

W.T. TOBIAS Counsel for Mr. & Mrs. Hines,  
(parents of deceased child  
Jordan Hines)

J.A. OLAH Counsel for Janet Brownless  
(Vereecken) R.N.A.

H. SOLOMON Counsel for Ontario Registered  
Nursing Assistants (other than  
those nursing assistants individually  
represented by counsel).

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---Upon commencing at 10:00 a.m.

THE COMMISSIONER: Mr. Lamek?

MR. LAMEK: Mr. Commissioner, I have as a witness this morning, and I have every expectation that he will be here for the day, Dr. David Seccombe.

DR. DAVID WILLIAM SECCOMBE, Sworn

DIRECT EXAMINATION BY MR. LAMEK:

Q. Dr. Seccombe, you are now based in British Columbia, but you were born and educated, at least to the Master's level, in Ontario.

A. That is correct.

Q. Touching very briefly upon the major milestones, you were graduated from the University of Western Ontario in 1967, with a Bachelor's Degree in Psychology.

A. That is correct.

Q. Subsequently from that same University, in 1974, a Master's of Science degree in Physiology.

A. Correct.

Q. Subsequently in 1981, you received a Ph.D. from the University of British Columbia in Physiology, but I understand the







1

2

doctoral project you undertook was biochemical in  
nature.

3

4

A. Heavily oriented to biochemistry,  
yes.

5

6

Q. Finally, in 1981; 1981 was a  
double year for doctorates for you; in 1981 you  
received a Doctor of Medicine Degree from the  
University of Calgary.

7

8

9

A. That is correct.

10

11

Q. I understand you are now indeed  
in title Assistant Medical Biochemist at the  
Shaughnessy Hospital in Vancouver.

12

13

A. That is correct, and Vancouver  
General.

14

15

Q. And Vancouver General, and  
working towards a Fellowship in Medical Biochemistry.

16

17

A. That is correct.

18

19

Q. You provided me with a copy  
of your Curriculum Vitae which discloses that you  
are the author or co-author of a number of articles  
on a variety of biochemical subjects and that you  
have presented research abstracts in several forums.

20

21

A. That is correct.

22

23

MR. LAMEK: I wonder, Mr. Commissioner,  
rather than embarrassing Dr. Seccombe any further

24

25





1  
2 with a recital of his accomplishments, whether I  
3 might mark the Curriculum Vitae as an exhibit.

4 THE COMMISSIONER: Yes. Exhibit 7.

5 ---EXHIBIT NO. 7: Curriculum Vitae of Dr. David  
6 William Seccombe.

7 MR. LAMEK: Q. Dr. Seccombe, our  
8 interest here obviously is in your most recent  
9 publication which I believe has been a letter to  
10 the editor of the New England Journal of Medicine  
11 which was published in the April 11, 1983 edition  
12 of that Journal and which was headed "Digoxin-Like  
13 Immunoreactivity in Premature and Full Term Infants  
14 Not Receiving Digoxin Therapy".

14 Perhaps you could identify that.

15 A. I would just correct you on  
16 the date. It is April 14.

17 Q. It is April 14, you are quite  
18 right. My tired old eyes don't work as well as  
19 they used to on small figures.

20 I am showing you a Xerox copy of  
21 the letter, just to make sure that we have the  
22 right one.

22 A. That is the correct one.

23 MR. LAMEK: I wonder if that might  
24 be the next exhibit, Mr. Commissioner?  
25







THE COMMISSIONER: Exhibit 8.

---EXHIBIT NO. 8: Letter to New England Journal  
dated April 14, 1983 re:  
"Digoxin-Like Immunoreactivity  
in Premature and Full Term  
Infants Not Receiving Digoxin".

MR. LAMEK: I should say that  
I made available that letter to other counsel on  
Friday. They may or may not all have it. I have  
extra copies here, as I have of all the material  
to which I propose to refer. I will have those  
distributed, and copies of Exhibit 7, the Curriculum  
Vitae.

THE COMMISSIONER: All right.

MR. LAMEK: Q. Dr. Seccombe, your  
Curriculum Vitae discloses no prior published work  
touching upon digoxin. Can you tell me, please,  
when and how your interest arose in digoxin leading  
to the research study which is summarized in the  
letter to the New England Journal?

A. I guess it is approximately  
a year ago a baby in Vancouver was transferred to  
Vancouver General Hospital and the presenting signs  
and symptoms of this infant were such that the  
admitting physician decided that there was a  
substantial likelihood that the baby inadvertently







1  
2 might have been treated with digoxin or in fact was  
3 digoxin toxic.

4 In order to rule this out of his  
5 differential diagnosis for the presenting signs  
6 and symptoms he ordered a digoxin level. There was  
7 no recording of any dosage of digoxin having been  
8 given to this baby.

9 A sample was sent to the lab. We  
10 returned a value of approximately, I cannot  
11 remember the exact figure, but it was about 1.5,  
12 1.5 being within therapeutic and certainly not  
13 toxic, and he was able to eliminate that as a  
14 possibility for the signs and symptoms that  
15 this baby was presenting.

16 In any event, he phoned the lab and  
17 made an enquiry as to why he should have an answer  
18 of 1.5 and yet there was no documented history  
19 of this baby having been given digoxin.

20 We then suggested that he wait  
21 for two weeks and repeat the blood level. Certainly  
22 we would expect digoxin to be cleared from the  
23 blood probably within six days of discontinuance of  
24 the drug if by chance the baby had been given  
25 digoxin inadvertently.

He repeated the blood sample two weeks





1  
2 later and we now got a value of 1.8 and we knew  
3 that during that two week period the child had not  
4 been given digoxin.

5 We then took that same sample and  
6 sent it to two other hospitals in Vancouver,  
7 St. Paul's and Shaughnessy Hospital, and requested  
8 the digoxin level from those two hospitals. Both  
9 hospitals reported an answer back that was  
10 significant, in other words above .2, but to our  
surprise all the answers were different.

11 Now if this child in fact had been  
12 given digoxin we would have expected all three  
13 methodologies to give us approximately the same  
14 answer. The fact that all three methodologies,  
15 which were different, gave us different answers,  
16 we then realized that we were probably dealing  
17 with some substance other than digoxin that was  
18 being recognized by the traditional digoxin method-  
ologies. That is how we became interested and we  
19 thought that all this insight should be pursued.

20 Q. Can you tell me, Doctor,  
21 what symptoms were being exhibited by this infant?

22 A. I'm not really in a good  
23 position to give comment on that. Dr. Whitfield,  
24 who is one of the co-authors of our letter in fact  
25







1  
2 was the physician who was involved in admitting  
3 this child. I am led to believe he had high  
4 potassium levels and cardiac arrhythmias.

5 MR. STRATHY: I am not getting all  
6 this. I know the witness is speaking into the  
7 microphone, but could he repeat that last bit, please.

8 THE WITNESS: Maybe I'm staying  
9 too close - I will stay back.

10 Just to repeat, basically I said  
11 that I do not think I am in a position to accurately  
12 detail the exact signs and symptoms that this baby  
13 was presenting. Dr. Whitfield would be in a better  
14 position to do that. He was the physician who  
15 admitted the child. If my memory is correct, I  
16 do believe the child had elevated potassium levels  
17 as well as cardiac arrhythmia, which would suggest  
18 digoxin but many other things as well.

19 MR. LAMEK: Q. You have no  
20 recollection of the particular variety --

21 A. No, I could get you that  
22 information if it is necessary.

23 Q. You say you referred the second  
24 sample to two other hospitals after you had recorded  
25 a level of 1.8 nanograms per millilitre.

A. That was approximately. I do





1  
2 not have the exact figures but I know it was  
3 greater than 1.5.

4 Q. And each of those other  
5 two hospitals reported levels in excess of 0.2  
6 nanograms?

7 A. Yes.

8 Q. Did either of the other reported  
9 levels approach your level of 1.8?

10 A. No, they did not.

11

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Q. Can you give me some idea of the order of those other levels?

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A. Well, basically -- the order of magnitude you mean?

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Q. Yes, please.

A. Basically there was one answer that was one-half of our original answer and one that was just slightly lower than one-half. So, they were all to the low side of our answer.

10

11

12

Q. But in each case, I take it, from what you have said, less than one nanogram per millilitre?

13

14

15

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A. No, in each case I think that for most of these methodologies the lower limit of sensitivity or the cutoff point is usually of a .2 and these tests can reliably measure values greater than .2. All of the answers that we received on this broad sample were all greater than .2.

18

19

20

21

Q. Yes, I understand, but you said one-half of your reading, which is 1.8, and therefore, I take it their levels were less than one nanogram per millilitre.

22

23

24

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A. Oh, yes. I thought you said .1.

Q. No, no, sorry. You said the





B-2

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other two hospitals used different methodolgies.

3

Were they all using the radioimmunoassay?

4

A. They were all radioimmunoassays.

5

Q. In what respect were the

6

methodolgies different, or do you know that?

7

A. Well, generally speaking, these

8

methodologies are not all that different, the basic

9

principle is the same, packaged a little differently

10

and the radio label may be different. I think the

11

major thing that one would be concerned about in

12

this particular case and the major variants between

13

the kits would be the antibody because they all do

rely on the antibody methodolgy.

14

Q. At that point in time, which

15

kit was your laboratory using?

16

A. We were using the NML Kit.

17

Q. NML Kit?

18

A. Yes.

19

Q. And the antibodies that came

with that kit?

20

A. That is correct.

21

Q. Do you know which kits were

22

being used by the other two hospitals to which you

23

referred the sample?

24

A. I know that Shaughnessy Hospital

25







B-3

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2

was using clinical assay methodology. St. Paul's  
I can't remember what kit they were using.

3

4

Q. But is your recollection that  
it was yet a third kit?

5

6

A. It certainly was a third kit.

7

Q. So, the differences were in  
the kits and the suppliers of kits?

8

9

A. That is correct.

10

Q. And the variations in  
methodologies that applied to each supplier's own  
kit?

11

12

A. That is correct.

13

Q. All right. So, Doctor, your  
curious state having thus been peaked, what did you  
do?

15

16

A. Well, as it so happened, I was  
invited to attend a research meeting regarding a  
different project that we had underway and at that  
time discussed the observation with Dr. Whitfield  
and together we decided we had better chase this  
observation. So, we then went to the premature  
nursery and collected some samples from 25 different  
infants in the intensive care nursery, none of whom  
had been given digoxin. There was no special  
selection process involved, there was just randomly

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B-4

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selecting 25 infants that were present and measuring digoxin in these 25 samples.

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Q. One thing I forgot to ask you about, the triggering incident. How old was the child from whom the original sample was taken?

7

8

A. This child I believe was approximately a month.

9

10

Q. One month?

A. Yes.

11

12

Q. And the ages of the children from whom you took samples for the purpose of the studies?

13

14

A. It is stated here in the letter. There was an age range of zero to 146 days.

15

16

Q. All right. Other than recording the age of the child from which you took this sample, I assume you did that?

17

18

A. That is correct.

19

Q. Were you concerned to select a range of ages?

20

21

22

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25

A. Initially we weren't. We obviously were concerned that that initial observation was an isolated observation and, so, the first phase of our program was really to substantiate whether or not that was an isolated event or in fact







B-5

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2

is this a commonly occurring event. So, there was  
no selection from age initially; later on we did.

4

5

6

Q. You say the first stage of  
the research. Does the letter which we have marked  
as an exhibit embody the results of the first stage?

7

A. Yes.

8

9

Q. So, you collected sample from  
25 children, not know previously to have received  
digoxin?

10

A. Correct.

11

12

Q. And whose ages range from 0 to  
146 days. Can you tell me what happened then?

13

14

15

16

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A. Well, basically we collect  
those samples. We measured them in duplicate using  
two different methodologies. The NML methodology,  
which had given us the highest answer initially and  
then the clinical assays methodology which gave us  
the second highest answer in the initial observation.

19

20

Q. Can I ask you to pause there,  
Doctor. You told me that at that time the method  
in use in your lab was the NML?

21

22

23

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A. That is at the Vancouver General  
Hospital. It is difficult because I worked at two  
labs. The other lab was using the clinical assay  
method, which is Shaughnessy.





B-6

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Q. All right, you answered my question, you had experience with both methods?

A. Yes.

Q. Good, thank you. So, you duplicated, that means you split each sample, when you say you duplicated each sample?

A. Yes.

Q. Well, these methodologies require very low volumes of sample in order to run

A. Yes. So, when I say we did it in duplicate, we would do it in duplicate with each methodology, so, each sample was in fact measured four times, two times with each method within run duplication; in other words, they weren't run on separate times but together within the same run.

Q. All right. On serum I take it?

A. Yes, that is correct.

Q. Can you tell me the on-going story of this?

A. Okay. So that initially we made this observation and we thought that certainly it should be published and we elected at that stage to send it as a letter and then ran into two kinds of problems getting it published because of the nature







B-7

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of the topic.

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It was initially sent to New England and back and forth and then finally New England decided to send it out for peer review prior to it being published and that delayed it by about three or four more months.

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In any event, it was published. After it was published we then tried to determine at what stage does this material disappear or become insignificant because I know that using these two methodologies I measured my own blood level of digoxin and I don't take digoxin and certainly the methods were both the same, I had no digoxin.

14

15

16

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Q. Doctor, again let me interrupt you. You were going on to determine what you did after the work which is recorded in the letter that we have before us at the moment?

18

19

A. That is correct.  
Q. I wonder if we could just stop with the letter for the moment?

20

21

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A. All right.

23

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25

Q. And deal with what you called the first phase of this project.

A. Well, basically I would say what the bulk of the first phase of our work is





B-8

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and what is encompassed in this letter. There was the initial observation, there then was a sample gathering of 25 samples. We have only reported a cross-range or cross-sampling of the 25 that we looked at. The article contained ten representative cases, there were 25 in total.

Initially as well we looked at a few older children, normal, healthy, greater than two months children.

Q. Let me be sure that I understand the table of the ten results that you do show on page two of the exhibit. You record ten samples, some of which are apparently from cord blood Can you explain that for us, please?

A. Well, after we had run a few of these samples we realized that we were quite confident that what we were seeing was not some artifact, that there was something in fact present, that it tended to be present in neonates. So, the next question is, when does it first appear and when does it disappear.

So, we felt that cord blood was readily available and we thought, well, let's measure it in cord blood and also in older children. So that we started to go from target group to either







B-9

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ends of the age range.

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Q. Cord blood being umbilical

4

chord?

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A. That's right. Mixed cord

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blood initially.

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Q. So you reported results, four samples of cord blood No. 3, 6, 8 and 9, two male, two female, and then you recorded the age and days and sex of the children from whom samples were analyzed and recorded in this table, their weight, weight at time of sample taken?

A. I believe that is correct, yes, it is the weight at the time of sampling.

Q. You have noted any abnormalities, observed abnormalities in those children under these conditions; you haven't noted any medications they may be on and then you have recorded the level measured on the RIA for digoxin using the NML methodology?

A. That's correct.

Q. And those numbers range from a low of 0.8 in the cases of patients 8 and 9, both cord blood samples, and interestingly twins, were they identical twins?

A. I believe they were.

Q. Up to a high of 4.1 nanograms per millilitre in the case of Patient No. 5, a four-day old female baby who was premature and had the other attributes listed in your table.

The 4.1 stands head and shoulders above any of the other results recorded on that page,





C.2

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and obviously is a startling result, is it not?

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A. Well --

4

Q. Well, one of the most startling things?

5

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A. Well, I guess the thing that

7

startled us about the magnitude of these answers, we were aware there was research going on in lower

8

animals and in fact in men as well, but typically

9

the levels in men for digoxinlike substances were

10

usually .3 or less. So I must admit I was not only

11

surprised to see the 4.1 but also the .8, it was

12

certainly higher than had been reported.

13

Q. And all the intervening levels as well?

14

A. Yes.

15

Q. Because all of those levels

16

with the possible exception of 4.1 fall within what

17

is commonly regarded as the therapeutic range of

18

blood levels for digoxin, do they not, and perhaps

19

even the 4.1 at the upper end of the range?

20

A. The .8 may be arguable, but

21

certainly they would be close to the therapeutic range.

22

Q. Certainly levels such as 2.2?

23

A. Yes.

24

25







C.3

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2

Q. 2.6?

3

A. Yes.

4

Q. 1.2 and 1.6?

5

A. Correct.

6

Q. And these in babies who had  
not received digoxin?

7

A. That is correct.

8

9

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13

14

Q. Is the presence of levels of  
something in the cord blood, and indeed I think you  
said the levels appeared to be showing up most  
dramatically in neonates, did those two observations  
suggest to you that there may be some maternal  
transfer of digoxin to these children. Did you make  
any inquiries as to whether the mothers had received  
digoxin?

15

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A. Yes. Actually all of these  
samples were obtained in our healthy delivery suites,  
our healthy, referring to the health, the status of  
the mother at the time of presentation and none of  
these women were on digoxin. We checked that out,  
but initially we looked at the maternal blood.  
Subsequent to this first phase of the study we have  
looked at many more cord bloods and in fact have gone  
from looking at mixed cord blood to a separate sample  
umbilical artery and maternal as well to see if there





C.4

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was any gradient between artery and vein, or mother and baby. We found basically that levels were always higher in baby than mother and there was not any gradient between artery and vein. There was a gradient that would indicate, or at least suggest that we were getting some placental transfer of this substance. We did record a .3 I think was the highest one that we were able to record which may suggest that the baby makes material and sends it back to mum, I don't know. Certainly if it were coming from mum you could argue that mum's levels would be equal to baby or in fact higher than baby.

13

Q. You told me a few minutes ago that you analyzed serum that you drew from your blood, from blood that you drew from yourself?

15

A. That is correct.

16

17

Q. And found what, a nil or a zero reading?

18

19

A. They were all below the lower limit of sensitivity for the methodology which was .2.

20

21

Q. Have you similarly analyzed blood samples drawn from non-pregnant or non-recent mothers?

22

23

24

25

A. Yes, because one of the technologists involved in our research projects has







C.5

1

2

used her serum repeatedly for some of our samples,  
so I guess in that sense we have, we know she is  
zero as well.

4

5

Q. And any levels that are below  
the level that you have talked about in relation to  
your own serum?

6

7

8

A. Oh yes, we are well below,  
non-detectable in fact.

9

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15

Q. You reported levels, as we  
have said to 4.1 nanograms per millilitre on the NML  
method kit and antibodies. You told me earlier that  
these same samples, or parts of the same samples  
were also assayed with the kit supplied by clinical  
assays. You refer to that in the opening paragraph  
of your letter, half way through the paragraph  
where you said:

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"We also analyzed these samples  
without a commonly used radioimmuno-  
assay kit, clinical assay, Cambridge,  
Massachusetts, the values obtained  
were approximately one-half of those  
obtained with the NML kit."

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If one were to reduce by half the levels recorded  
in Table 1 in your letter, I take it most of those  
results would still be in excess of those previously





C.6

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recorded or believed to exist as a cross-reactive  
substance in the blood of someone who has not  
previously had digoxin?

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A. Yes. I would say that there  
may be some question with the .4, but generally  
there seems to be a trend to the higher end, yes.

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Q. So fairly, although the levels  
recorded by NML are more dramatic because they are  
higher, nevertheless even those recorded by the  
clinical assays method were, may I say, surprisingly  
high?

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A. We were very interested in them,  
yes.

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Q. Do you have any explanation  
for the variation in the results as between those  
two methodologies?

A. Well, certainly the ability  
to measure digoxin in blood is a function of your  
antibody, and the fact that the -- let me just back-up.  
Let us assume that we were measuring digoxin in 25  
people that had normal kidney function and were being  
treated with digoxin and we used these two methodologies.  
We would see values that would be almost identical  
using the two methodologies. The fact when we did  
our sampling of 25 infants the fact that the two





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methods were giving us very different answers suggested that the antibodies in these two methods were cross-reacting with some other substance that was present in the bloodstream of these babies, that was not digoxin, but probably had great similarities to digoxin. So the difference really comes down to antibody and its ability to recognize digoxin and only digoxin and to be able to discern the presence of digoxin and separate its presence from Substance X or whatever you want to call it.

Q. That is a good term for it. Let me be clear, Dr. Seccombe, it is not part of your thesis as set out in the letter which we have marked as an exhibit, that the substance that you were recording on the assay was digoxin?

We are quite confident that it's not digoxin.







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Q. Whatever it is, it is a substance that in one way or another, and you can talk about that in a moment if you would, binds with, clings to, the antibody used in the digoxin assay.

A. That is correct.

Q. And we have heard that there are certain known substances, in particular some of the metabolites of digoxin, which are chemically sufficiently similar to the digoxin molecule that the antibodies used in these assays cannot distinguish between them?

A. That is correct.

Q. Are you suggesting that substance X is another such substance, which the antibody cannot distinguish from digoxin, or distinguishes with varying levels of precision according to the antibody you use.

A. That is correct. But until we isolate it and purify it I have to assume that it is not digoxin. I am quite certain it will not be, it will be different in structure, but very similar probably to digoxin with minor variations.

Q. I am puzzled by one thing, Doctor. If the clinical assay's antibody does take up substance X to any degree that suggests, does





D-2

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it not, that even the clinical assay's antibody cannot distinguish between digoxin and substance X?

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A. Yes, it really comes down to the relative degree of cross-reactivity between the antibody and substance X. In the case of the NML antibody, that particular lot number that we used, the degree of cross-reactivity was approximately twofold greater than in the case of the clinical assay's methodology.

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Q. In other words, it is not simply a question of a substance being cross-reacted with an antibody. There are different levels cross-reactivity?

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A. That is correct. You could argue that you would have an antibody the next week that would cross-react with substance X to a much lower degree than the previous week, or, alternatively, the NML antibody may be picking up only ten per cent of substance X, and I might end up with an antibody a week later that would pick up 20 per cent of substance X. So it is a function of antibody cross-reactivity to substance X.

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Q. What appears to emerge from your having used the two methodologies on the samples is that there is a higher degree of cross-reactivity







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between the antibodies you were using at this time from NML and substance X than there is between the antibodies in the clinical assay's kit you were then using.

A. That is correct.

Q. Have you tried assays on these or other samples using other suppliers of kits, either instead of or in addition to clinical assays and NML?

A. Yes, we have. We have recently submitted a paper for publication to Clinical Chemistry which we expect will be published in the near future, but in that paper basically we measured 30 samples, using seven different methodologies including NML and six others.

Q. Kits supplied by seven different suppliers?

A. Yes.

Q. I recognize that in a pre-publication phase, you should not be publishing the paper itself, but can you summarize the results of these comparisons for us.

A. Basically we found in the seven kits that everyone of them shows some degree of cross-reactivity with substance X. In other





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words, all seven of them measured to varying degrees substance X; but there was quite a variation in the mean level that one would measure. The NML methodology was still giving us the highest answer and everything else was below that. And for this 31 sampling, the size of the mean value for the NML kit was 1.3. The other kits ranged from a low of .19 up to .94. So the NML methodology in that particular antibody that we had was measuring substance X more efficiently than the other kits.

Q. All right. Does it follow from that, Doctor, that one may minimize the recording of substance X, and the consequent possibility of distortion of digoxin levels recorded in IRA by using that kit which produced your lowest level of cross-reactivity on that study?

A. Certainly you would minimize the interference but we found substance X fluctuates from day to day as well so we have other variables that have to be taken into consideration, but certainly the lower the cross-reactivity the better off you are going to be.

Q. Once having established, as you did, the relative cross-reactivities of the seven kits that you used, could you have any





D-5

1  
2 confidence that they will stay ranked as you were  
3 able to rank them on that occasion.

4 A. Actually, no. We subsequently  
5 have checked other antibodies from the NML company  
6 and obviously we have stockpiled as much of the  
7 antibody that gave the highest cross-reactivity for  
8 future research purposes.

9 Subsequent antibody lot numbers from  
10 the company have resulted in lower degrees of cross-  
11 reactivity. In fact, the last figure here in our  
12 paper actually demonstrates this fact, it looks  
13 as though the subsequent lot of antibody gave us  
14 about one-half the degree of cross-reactivity as  
15 observed in the first lot of antibody. We phoned  
16 the company to find out what was happening and they  
17 said they had gone to a different rabbit for that  
18 antibody lot. So obviously it is a function of  
19 antibody lot and it can fluctuate within a company  
20 on a lot to lot basis.

21 Q. So there may be varying degrees  
22 of cross-reactivity as between different suppliers  
23 of antibodies and even as, at least on this occasion,  
24 between different lots of the antibody supplied by  
25 the same supplier?

A. That is correct.







D-7

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of age but yet premature, the material will still  
be around.

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Q. You recorded in the letter to  
the New England journal at the end of the first  
paragraph:

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"Full-term infants older than two  
months did not have high levels of  
this immunoreactive digoxin less than  
.2 ng per milliliter."

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A. That is correct.

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Q. With respect to premature  
babies, is there any indication that although they  
may have levels higher than those recorded in the  
well babies after two months after birth, in terms  
of elapsed time from conception there may be some  
correlation between the observed decline in values?

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A. I would say that would apply  
to the healthy infant, yes. I am not so certain  
that it applies to a sick baby or a premature baby.

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22

23

Q. Do the data that you have  
collected to date, Dr. Seccombe, suggest that the  
presence of substance X in concentrations greater  
than .2 nanograms per millilitre is to be expected only  
in the early developmental stages of a baby's life.

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A. I guess I would have to say,





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Q. Let me go back to the age of babies for a moment, and I think at this stage I do need to let you take us beyond the first phase of the study.

Did I understand you to say that in the first phase of the study the observation was that perhaps substance X was either more likely to be found in significant concentrations in neonates?

A. Certainly that was our target group and that seemed to be the indication.

Q. What did you do to follow that up?

A. As I alluded to earlier briefly, we obviously then wanted to establish the fluctuations of this material relative to ages, relative to weight, on a day to day basis and within day to see whether or not this substance fluctuates within the day and on day to day. So we set up appropriate sampling procedures to answer those questions.

Q. Is that study still going on?

A. We have preliminary data, it is not published yet. We have indications that material in healthy, well, full-term infants tends to reach negligible levels by two months of age but yet if you take a premature baby at maybe two months







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no, because there is other evidence in the literature now recently published that would suggest that, at least indirectly suggest, that this same material may be appearing in certain pathological conditions in adulthood. So I think it all depends on the relative health of the individual and what the particular pathology is of an individual.

Q. I guess you have us at this, among other, disadvantages, Doctor, that your Table 1 in the letter records only the results from 10 of the 25 patients sampled, and of the 10 the diagnosis, other than for cases of two of the cord blood records septicemia, infection, a variety of indispositions. Can I put it that way?

A. That is correct.

Q. Are the 10 a representative sampling of the 25?

A. We felt that they were. We were not trying to zero in on any specific group but rather casting our net as wide as we could to see what sort of patterns could be established.

Q. I asked that, because of the ten samples recorded in Table 1, the oldest is of age 50 days and therefore I have to take it that the observation at the end of paragraph one of the





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letter, that full-term infants older than two months did not have high levels of this immunoreactive digoxin, must be based upon observations from one or more of the other 15?

A. That is correct.

Q. Therefore I need to know what the well or unwell state of the other 15 was. Are these ten representative in general terms of health, indisposition, wellness, or illness?

A. We were quite confident that they were. They were samples that were submitted by an out-patient pediatric department at the hospital, children, young infants coming in for medical checkups for one reason or another.

Q. So may I take it then that this whole group of children had generally some greater or lesser degree of indisposition? I do not think there is anything wildly serious recorded here by way of diagnosis.

A. There babies were all sufficiently sick to be in the premature nursery.

Q. And therefore even in that population your observation was that levels of substance X declined to less than .2 nanograms per millilitre after two months, in full-term babies.





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A. In full term healthy babies that were not in the nursery.

Q. When you say healthy babies that you sampled, as you have just told me, your population was of children who were sick enough in one way or another to be in the hospital?

A. I think where we're getting a little confused here is that the 25 sample end value for this particular study was all drawn from the nursery. None of that end value of 25 were greater than 2, would be classified as a healthy full term infant.

The statement that refers to full term infants older than two months did not have high levels of this immunoreactive digoxin and that represented a small sampling of five to ten infants that were part of the Out-Patient Pediatric Department that we analyzed for digoxin-like substance.

Do you understand that?

There were 25 premature infants.

Q. Yes.

A. In the nursery that formed the bulk of this study. This statement that refers to the infants older than two months refers to another small study involving five to ten







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out-patient samplings of healthy children.

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Q. All right.

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A. All right.

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Q. The final sentence of that

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paragraph then is based upon data recorded in  
samples from children other than the 25?

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A. Yes, I'm sorry.

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Q. Referred to in the first part

9

of the paragraph?

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A. That's right, that's right.

11

Initially we made this observation we thought,

12

let's go to the other extremes of the line here and

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see just exactly when we lose this. So, I made

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arrangements to collect five, ten samples from

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healthy well children that were presenting at

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the clinic.

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Q. Okay, Doctor, but even there

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I have to observe that you say in the first part  
of the paragraph:

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"We analyze serum and cord blood from

20

25 premature and full term babies,

21

age range zero to 146 days."

22

A. Yes.

23

Q. Of the ten whose results and

24

characteristics are recorded in Table 1, the oldest

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is 15.

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A. That's right.

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Q. And therefore some of the older

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children must be among the other 15?

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A. Exactly, right, yes.

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Q. 15 people who are in-patients?

8

A. That's correct, yes.

9

Q. And therefore among those you

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must have been able to make some observation as to

11

whether these levels declined in babies who were

12

at least sick enough to be in the nursery at the  
hospital?

13

A. Well, those ones I can assure

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you were all greater than .2.

15

Q. All right.

16

A. All right. So, we have a sick

17

baby that may be 146 days old in the premature

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nursery, i.e. greater than two months of age but

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sick, would have levels greater than .2. We take

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a comparably aged child who is out, healthy, well,

21

at home with mom, we get values less than .2, or  
insignificant.

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Q. Okay, I just want to understand.

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Of the over two month old but sick babies who retained

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levels greater than 0.2 in the nursery, were they all

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premature or was any of those full term babies?

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A. Most of the babies were

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premature. I would have to go back and get out the

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specifics, Mr. Lamek. I must admit, that's my

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feeling that they were premature.

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Q. My concern is to understand

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what limitations or qualifications have to be

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placed on the final sentence in the first paragraph

10

of the letter. You understand what I'm getting at  
right now?

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A. Yes.

12

Q. Okay. Was any attempt made

13

to separate substance X out of the samples by use

14

of a process of which we have heard here, high

15

pressure liquid chromatography?

16

A. Certainly we plan to do that

17

in the very near future.

18

Q. It has not been done?

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A. It has not yet been done.

20

Q. Okay, expensive equipment and  
procedure I take it.

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A. Well, I have a grant pending

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which that forms part of the proposal.

23

Q. But clearly that would be a

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desirable thing to do, would it not?

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A. Certainly I think that if we could separate X from digoxin it would facilitate things quite a bit.

Q. But important to know even if you can't separate it?

A. That's true because it would facilitate isolation and purification of the material, yes, quickly.

Q. Yes. Now, Doctor, you've referred to other work along similar lines as being done. It appears, if I may say so, to be the sort of glamour project this year for the biochemical world. You're aware, are you, of other articles that have appeared in the last two or three months of reporting on studies similar in structure to the one you have just described?

A. Yes, I must admit I've been away on a holiday, so, you have given me three that I have had an opportunity to read.

Q. Okay. I think you have only very recently become aware of an article in this month's issue of the Journal of Pediatrics by Valdez and Brown entitled "Endogenous Substance in New Born Infants Causing False Positive Digoxin Measurements".

A. That's correct.





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Q. Essentially the same kind of  
conclusional finding that you arrived at?

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A. That's right.

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Q. All right. And as I read that  
article, Doctor, you may not have had a chance to  
consider it closely yet and I don't mean to be unfair,  
but as I read it, four RIA kits, methodologies were  
used in that study, including the kit of clinical  
assays. Assays conducted on all of those kits,  
with all of those kits recorded the presence of a  
digoxin-like substance that was cross-reactive to  
one degree or another with the RIA antibodies in  
the kit, but as I read the results that are recorded  
on page 2 of that article, and I have copies of this  
article for counsel if they have not yet been made  
available. Perhaps I will just wait a moment until  
everybody has a copy. Do you have a copy,  
Mr. Commissioner?

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THE COMMISSIONER: No.

19

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MR. LAMEK: Perhaps I can mark a  
copy and you can have it.

21

THE COMMISSIONER: Yes, Exhibit No. 9.

22

---EXHIBIT NO. 9: Article in the Journal of  
Pediatrics by Valdez and Brown.

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3 MR. LAMEK: Q. The second page of  
4 the Xeroxed copy of the article, Doctor, there is  
5 Figure 1 and in the left hand side of which is a  
6 recording of the levels from a digoxin RIA in adult  
7 controls and on the far right hand side the levels  
8 recorded in amniotic fluid and then the centre block  
9 of the figure records the levels obtained by the  
10 use of the four methodologies there, supplies are  
11 identified on the first page of the article.

12 As I read the article, some 135  
13 children were sampled in all, new born infants aged  
14 between 2 and 4 days, and it appears from Figure A,  
15 does it not, that the highest recorded level was  
16 by Method A, which, interestingly, was clinical  
17 assays, one of the methodologies used by you, and  
18 was essentially 1.4 nanograms per millilitre; most  
19 results being, indeed all but four results being  
20 under one nanograms per millilitre, if I read the  
21 table correctly, or the figure correctly.

22 I would be grateful for your  
23 confirmation that I am so reading it correctly.

24 A. Yes, yes.

25 Q. Because I have little confidence  
that I am.

A. Yes.







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Q. Okay. So, in its nature, the same sort of observation that you have made and recorded in the letters of the New England Journal, but at levels rather lower from those measured by you?

A. By the NML methodology?

Q. Yes.

A. Yes.

Q. Consistent though I take it with your clinical assays results.

A. Certainly not out of line with it.

Q. Next, Doctor, there is earlier this year in an edition of Clinical Chemistry, a very brief abstract or report, a study conducted by Hicks and Brett of the Children's Hospital National Medical Centre, George Washington University School of Medicine and Health Sciences in Washington, D.C. entitled "Falsely Positive Digoxin Results in Serum Specimens from Acute Care Infants". I have recently brought that to your attention, have I not?

A. That's correct.

MR. LAMEK: May that be the next exhibit, Mr. Commissioner?

THE COMMISSIONER: Exhibit No. 10.





1  
2 ---EXHIBIT NO. 10: Study entitled "Falsely Positive  
3 Digoxin Results in Serum Specimens  
4 from Acute Care Infants" by  
5 Hicks and Brett.

6 MR. LAMEK: Q. Now, that is a very  
7 brief report and apparently samples were drawn from  
8 acutely ill or premature infants of less than six  
9 months of age and from children between the ages of  
10 six months and 16 years.

11 I must confess, I'm not clear on the  
12 rather terse report that appears here whether the  
13 children of six months to 16 years were also acutely  
14 ill or had been premature. Nevertheless, we can  
15 take it as we read it, I suppose. It is recorded  
16 that that:

17 "All of the samples from the children  
18 six months to 16 years yielded negative  
19 results (less than 0.1 nanograms per  
20 millilitre) for digoxin using all  
21 six kits."

22 A. That's right.

23 Q. With respect to the infant  
24 samples there were positive results in three of the  
25 kits apparently concentrations of digoxin, can we  
say recorded levels of something?

A. That's right.





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Q. Ranged from .2 to 2.9 nanograms per millilitre and the suggestion I take from this, Doctor, is that substance X is shown up in these children under six months of age. Is that a reasonable inference to draw from this?

A. Yes.

Q. Children had not been previously on digoxin and, therefore, I take it you would agree that what is being measured is not digoxin but a cross-reactive substance?

A. That's correct.

Q. But again demonstrating the variation that is observed not only between children of different ages but between different immunoassay kits?

A. Correct.

Q. And the third of the research reports hot from the press, which I have mentioned to you, is again an extract presented at the Second International Congress on Pediatric Laboratory Medicine, that Congress having been held here in Toronto, May 29th, to June 2, 1983.

THE COMMISSIONER: Exhibit 11.

MR. LAMEK: Thank you,

Mr. Commissioner.







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2 ---EXHIBIT NO. 11: Document entitled "Second  
3 International Congress on  
4 Pediatric Laboratory Medicine".

5 MR. LAMEK: Q. And once again in  
6 the rather terse abstract that is there presented  
7 under the heading "False Positive Digoxin Results  
8 in Infant Sera with Some Commercial RIA Methodologies:",  
9 the authors being Danzer, Pratt, Lewis and Chandramouli.  
10 Again, there is indication that levels of something  
11 that was cross-reacting with the digoxin antibody  
12 in RIA was recorded in children who had not received  
13 digoxin.  
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And different kits, methodologies were used there,  
and also the fluorescence immunoassay, are you  
familiar with that technique, Doctor?

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A. Very limited knowledge of it,  
it is a new methodology I know brought out by  
Abbott's Laboratories.

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Q. But again operates basically on  
the --

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A. It is an antibody based  
methodology.

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Q. Immunology principle.

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A. That's correct.

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Q. Antibody attraction.

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A. Yes.

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Q. And again variations between  
different methodologies. The results are rather  
interesting although the overlapping ages of some  
of these children may cloud the issue a bit. The  
highest level recorded appears to be in cord blood,  
their mean level that is, .67 nanograms, followed  
by levels recorded in the serum samples taken from  
infants zero to 14 days, less than half a nanogram,  
and third maternal, serum samples .38 nanograms.  
There certainly does appear to be a decline in the  
mean levels recorded as the ages of children advance,





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is that a fair observation?

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A. That fits with our observations

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as well.

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Q. So, Doctor, as I say this seems

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to be the hot topic in biochemistry this year, and

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clearly arrived at what I think is called the cutting

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edge of all. There seems to be a fast

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growing body of research data to establish the

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existence of what we are calling substance in X in

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very young children. Such disagreement as there may

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be between the results goes to the levels that are

being recorded, does it not?

13

A. That is correct.

14

Q. And those you have told us may

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be dependent upon methodology that is used for the

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particular sample, and we have certainly seen

variations between them.

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A. It would be dependent upon

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antibody cross-reactivity, yes.

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THE COMMISSIONER: What is the

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significance of the third column, what does that

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stand for?

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THE WITNESS: This is in which

particular --

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THE COMMISSIONER: It is on this --

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THE WITNESS: This last page?

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THE COMMISSIONER: On Exhibit 11.

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MR. LAMEK: It is an abbreviation

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in number.

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THE COMMISSIONER: What does this

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Std.Dev.N, what do they stand for?

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THE WITNESS: N refers to the

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sample size and the standard deviation is a

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statistical term that gives you an indication of

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the degree of scatter that one obtained with the

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16 samples that were measured.

THE COMMISSIONER: Thank you.

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THE WITNESS: And typically the

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95 per cent of the observed population would fall

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within two standard deviations of the mean.

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MR. LAMEK: Q. When you say N is

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the sample size, you mean number of sample?

A. That is correct.

18

Q. That falls within the group

19

described in the last column?

20

A. So they did 16 cord bloods.

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Q. Dr. Seccombe, at least with

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the NML kit you seem to be leading the field in

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levels recorded?

A. That is correct.

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Q. Is the variation in cross-reactivity of different antibodies from different suppliers sufficient in your observation to account for the spread between the kind of levels we have seen recorded in the papers to which we have just referred, and the levels recorded by you in the letter to the New England Journal?

A. Yes, certainly.

Q. You don't see any inconsistency between your NML results and the other results?

A. No, in fact it is comforting to see that with the clinical assay methodology we are very close.

Q. What then is the value of the NML levels?

A. In what respect?

Q. Well, in the sense that they seem to be, they seem to tower over the other methodology levels, they are twice those in your experience of clinical assay.

A. Yes.

Q. And other results appear to be more closely akin to the clinical assay levels than to the NML levels, what is the value therefore of the NML levels?





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2  
3 A. Well, from my own personal  
4 point of view the value is you have an antibody  
5 that has a high degree of cross-reactivity and  
6 therefore is a very potential and powerful research  
7 tool to isolate this factor or substance. It may have  
8 just been fortuitous that at the time we made our  
9 initial observation we had an antibody in-house  
10 that was able to detect this substance more  
11 efficiently than some of the other methodologies.

12 Q. Unless we may be thought to be  
13 saying anything critical of NML and its product,  
14 it is fair to record that a subsequent lot of NML  
15 produced a measure of cross-reactivity that was  
16 apparently close to those of the other kits used.

17 A. That is correct and I know they  
18 are actively pursuing this topic themselves and trying to  
19 reduce the degree of cross-reactivity.

20 Q. Is the message this, Doctor?  
21 Until such time as one can identify, isolate and  
22 separate out substance X, the purpose of performing  
23 an RIA for digoxin, one has to be aware of:

24 (a) its recorded presence in these  
25 studies that have appeared; and

(b) the element of variation that  
may occur from kit to kit and to have some feeling







1  
2 for the cross-reactivity of the kit one is using,  
3 is that fair?

4 A. That is fair, that is correct.

5 Q. In an applied sense is that  
6 the significance of the NML results even?

7 A. Yes. I would also then  
8 mention though, that even given that you have the  
9 other variable as well which is the patient variable,  
10 because we find it can fluctuate quite substantially  
11 from a day to day basis.

12 Q. Absolutely. Now, accepting  
13 your results and of course we do and those obtained  
14 in the other similar studies to which we have  
15 referred, what is the significance of this research  
16 in terms of monitoring of digoxin levels in a  
17 clinical setting, forensic measurement of digoxin  
18 levels, what is the significance of what you have  
19 produced to date, Doctor?

20 A. Well, let's begin with the  
21 clinical significance, I think that basically what  
22 it does is it at some level invalidates the  
23 therapeutic drug monitoring of digoxin in this  
24 particular age group until such time as we can  
25 develop a method that is selective for digoxin and  
only digoxin; i.e. can recognize and separate digoxin





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from our substance X.

Q. You say it invalidates?

A. Well, this basically means that if a doctor is going to titrate his drug level based on a laboratory measured value of digoxin it can create all kinds of confusion, and I have had experience with that certainly in Vancouver where a physician had titrated his digoxin in a baby using the clinical assay methodology and Shaughnessy Hospital ran out of kits and so the sample inadvertently was sent to Vancouver General where the NML method was being used. According to the clinical assays method the baby was right within therapeutic range; according to the Vancouver NML result the baby was grossly toxic and the physician was going crazy and didn't know quite what to think of it.

Q. Can I just ask you one explanation. You say titrate his blood level, you mean fix his --

A. Yes, initially when you dose these babies you give them a little and you measure a level and you follow it for a few days, and assuming continuance of normal renal function and you have your blood level within a measured therapeutic window that you assume it will remain there if the





1  
2 dose is kept constant on a day to day basis. So  
3 that is titrating and it usually takes one or two  
4 measurements just to be certain that you have the  
5 baby within that range. So clinically it is really -  
6 certainly within the therapeutic range, it is a  
7 real problem. Because, for instance if your method  
8 is measuring a base line level of 4 and you come  
9 along and decide you are going to titrate to a  
10 level of 3 with digoxin and you don't know the baby  
11 has a 4, you are going to end up with a 7, and it  
12 is problem. Or you may titrate to a 3 and then get  
13 your 4 later on and end up with the 7, so it is  
14 a problem. Forensically I guess it comes down to  
15 the magnitude of substance X, how high can it become,  
16 what are the factors that regulate, or can determine  
17 the levels of X, and indeed where does X come from,  
18 is it produced by the body or is it coming from  
19 somewhere else.

18 MR. LAMEK: Doctor, I think those are  
19 all my questions. I wonder, Mr. Commissioner, if it  
20 might be appropriate to take the morning break at  
21 this stage to enable counsel to consider what they  
22 may want to do.

23 THE COMMISSIONER: I take it  
24 Dr. Seccombe is not coming back?  
25







1  
2 MR. LAMEK: Dr. Seccombe is not  
3 coming back, although I hope if it is absolutely  
4 necessary he may be available tomorrow morning. I  
5 have spoken to Dr. Seccombe and he is agreeable to  
6 spending time now before cross-examination with  
7 counsel, in an informal way, to clarify anything  
8 that he may have said and to assist them in under-  
standing the preparation of cross-examination.

9 THE COMMISSIONER: Well, I might  
10 take a vote on this matter. I don't know how well  
11 the system worked yesterday. Would counsel like  
12 a session, a private session that is without the  
13 reporter and without me? Would they at the same  
14 time also like to have - how long is Dr. Seccombe  
15 prepared to tolerate this?

16 MR. LAMEK: I would think we would  
17 not need to meet as long as we did last night with  
18 Dr. Mirkin. Dr. Mirkin spent an hour with counsel  
19 and his evidence lasted considerably longer and  
20 covered a greater field than Dr. Seccombe's. I  
21 don't know, I need to be told how long, certainly  
not longer than Dr. Mirkin was required.

22 THE COMMISSIONER: Can we have some  
23 comments from counsel as to what they want?

24 MR. LAMEK: There may be no interest  
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indeed in doing any such thing.

THE COMMISSIONER: Mr. Marshall?

MR. MARSHALL: I never turn the  
opportunity down.

THE COMMISSIONER: No. All right,  
well, what about, we will try it for half an hour.

MS. GOODMAN: If I may comment,  
Mr. Commissioner. I was at the meeting last night  
and I did find it quite useful. However, I did  
also feel that most of the information that we  
received from Dr. Mirkin last night would have been  
properly put on the record, but it did add to our  
understanding. So the only thing I am concerned  
about is certainly we can take that time but then  
we may come back and have to repeat everything on  
the record.

THE COMMISSIONER: If that is what  
happens then there is no point in having it at all.  
The only purpose is to shorten the cross-examination,  
that's all. If it doesn't work we won't have it any  
more.

Mr. Marshall seems to think it is of  
some assistance and you think it isn't, is that what  
I understand?

MS. GOODMAN: Essentially I did





1  
2 feel with respect to what happened last night that  
3 we would want to repeat a great deal of that on the  
4 record, now perhaps other counsel don't agree with  
5 me.

6 THE COMMISSIONER: Is there a  
7 difference between a great deal and all of it? If  
8 we are going to save any time I want to do it, if we  
9 are not going to save any time I don't want to, it  
is as simple as that.

10 MR. MARSHALL: The greatest benefit  
11 I think will be that we will all discover how  
12 stupid our questions are and what not to ask.

13 THE COMMISSIONER: If you discover  
14 that that will help then we won't have those questions,  
15 but if it isn't a help then we will forget about it,  
16 it is a little early to write it off. I think we  
17 will try it. I suggest perhaps now we take a break  
until - what do you think, 12 o'clock?

18 MR. LAMEK: I think if we were  
19 to come back at noon that should be ample time and  
20 sit in the normal way until lunch time.

21 THE COMMISSIONER: We will come  
22 back at 12 o'clock. Where would Dr. Seccombe be?

23 MR. LAMEK: We can be in a room  
24 right behind here and counsel can come right back.  
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THE COMMISSIONER: Yes, all right.

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You understand of course I will not be there and

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you understand the reporter will not be there so what

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you get is only - until it comes out is only at your

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own level.

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---Recess taken at 11:15 a.m. until 12:00 p.m.

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---Upon resuming

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THE COMMISSIONER: I am not asking for a verdict, but the question is, was there enough time, should there have been more or should there have been less?

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MR. LAMEK: I think it was about the right amount of time, Mr. Commissioner, you know, there is never quite enough. In terms of a verdict, I would like to speak to counsel possibly at the end of the day today to see what their reactions were. Certainly it was an interesting 45 minutes; whether it served to achieve the end that you desire, I do not know. Time will tell.

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THE COMMISSIONER: You have finished?

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MR. LAMEK: I have finished, yes, thank you, Mr. Commissioner.

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THE COMMISSIONER: Have you given any thought, gentlemen, as to who is to go first? Can I call on you, Mr. Brown?

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MR. BROWN: Yes. I have only a few questions.

THE COMMISSIONER: You are happy to proceed? All right, if no one else is claiming the honour.

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MR. BROWN: I have just been informed





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2 by Mr. Strathy that that is not the previous order.

3 MR. MARSHALL: I can go first, rather  
4 than argue about it.

5 MR. BROWN: If that is not acceptable,  
6 I will be quite happy to go first.

7 THE COMMISSIONER: I think, Mr. Brown,  
8 we will take you. What I am going to do is any  
9 time that anyone wants to agree to letting someone  
10 go first, that is fine by me, any order that you  
11 want. If I don't, I will just call on you or  
12 whoever is in your position first and go on ,  
just taking them in order.

13 All right, Mr. Brown, you can proceed,  
14 then.

15 CROSS-EXAMINATION BY MR. BROWN:

16 Q. There are simply two areas  
17 that I would like to explore with you and the areas  
involve the use that we can make of your studies.

18 MR. LAMEK: Mr. Commissioner, forgive  
19 me, I wonder if Mr. Brown would be good enough to  
20 go to one of the microphones.

21 MR. BROWN: Yes, certainly.

22 Q. The first area that I would  
23 like to explore, Doctor, if you could assume a child  
24 who to your knowledge has not been administered  
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2 digoxin, not on digoxin treatment, and you take a  
3 premortem sample of blood and as a result of a RIA  
4 test, let us say, the highest one that you have used,  
5 this NML test, you have a reading of 30 nanograms per  
6 millilitre. Your study, I take it, it is fair to  
7 say, has shown on children of a certain age and a  
8 certain medical condition, that is, they are pre-  
9 mature and very young, that you have found by using  
10 the RIA technique a certain background level which  
11 is detected when you are using the RIA method and  
12 this background level can range anywhere from  
13 something greater than 0.2 nanograms to approximately  
14 4.1 nanograms, an average of somewhere around 1.4  
15 nanograms.

16 Is that a fair statement?

17 A. That is fair.

18 Q. If we go back to my hypothetical  
19 example of this child who, let us assume, is young,  
20 born prematurely, not in good health, there is a  
21 premortem blood reading during when the child is  
22 young, the reading discloses a finding of 30 nanograms  
23 per millilitre. How do you use your study to  
24 interpret that finding of 30 nanograms per millilitre?  
25 Do I simply take perhaps the highest level that you  
found as a background level 4.1 nanogram, subtract  
that from my reading of 30 nanograms to give me a truer





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finding of approximately 26 nanograms per millilitre.

A. Ideally you would want to be able to determine what portion of your 30 value represents the drug digoxin and the substance X.

To my way of thinking, until we know what are the factors that determine the levels of substance X, and I think the only way you can really make a statement as to the relative contribution of each would be to separate the two and quantify them separately.

Certainly we have not recorded levels anywhere up to the 30 in blood of our substance X, but we have to keep an open mind. I have absolutely no idea what are the factors that dictate our levels of X and what conditions would lead to extraordinarily high levels of X. Maybe there are none. I just don't know.

Q. Without want to pin you down, without you having done the research into quantifying the substance X, is it then fair to say that the only use that we can make of your study right now is that if you do have a certain reading with the IRA methodology that that reading has to be qualified by what appears to be a factor of anywhere from slightly less than one nanogram to perhaps as high





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as four nanograms and that within that range there may be a detection of a substance which is not digoxin.

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A. That would be, with the state of the knowledge today, that certainly would be a good summary.

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Q. So if we go back to my original hypothetical situation where we have this extraordinary reading of 30 nanograms, would it be fair to say that the most you would want to venture at this point is that faced with the reading of 30 nanograms per millilitre and in view of your study we might have to qualify or reduce that finding by a certain factor, recognizing that part of that reading may reflect the detection of a substance other than digoxin?

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A. Correct.

Q. If we can move on then to a

second hypothetical, a child who is on digoxin and is known to be on digoxin, again in the same age group and the same clinical group that you are examining, a premortem blood sample is taken and again a certain reading is found, let us again assume 30 nanograms per millilitre, can I make the same use of your study as I suggested previously, that is to say that







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in a child who is known to be on digoxin we must qualify the digoxin reading obtained from an RIA study by a certain factor recognizing that that factor perhaps reflects the identification of some substance other than the drug digoxin.

A. I think that is a true statement, yes.

Q. So you would apply the results that you have found not only to children who are known not to be on digoxin treatment but also to children who are known to be on the therapeutic digoxin treatment?

A. Yes.

Q. At the present stage you would be willing to qualify any RIA result that you obtained by a factor of somewhere between greater than 0.2 and 4.1 nanograms per millilitre?

A. Given the current state of knowledge.

Q. Given this current state of knowledge?

A. Yes.

MR. BROWN: Thank you, those are all my questions, Doctor.

CROSS-EXAMINATION BY MR. STRATHY:





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Q. Doctor, I was not entirely clear from your resume' and your evidence in chief exactly what it is you do when you are not writing learned letters to editors and not giving evidence in these proceedings. Can you tell us a little bit, please, sir, about what exactly you do in the hospital?

A. Officially I am classified as an assistant medical bio-chemist, and I am in charge -- over the last two years I have been in charge of quality control at Shaughnessy Hospital laboratory. I have been actively involved in establishing new methodologies involving high pressure liquid chromatography. I think 15 per cent of my time is also with the University of British Columbia, Department of Pathology, as an Assistant Professor. I do some teaching. I am more or less responsible for helping to oversee the running of the medical bio-chemistry lab and as well have an active research component to that job as well.

Q. You engage in your own research, then, or research with others?

A. Very much so.

Q. Do I take it then from what you've said that much of your day to day time is in





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the laboratory?

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A. Yes, right at the bench.

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Q. Was it in the course of being

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in effect at the bench that you made this first

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discovery?

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A. No. It was, as I mentioned

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earlier, it was basically initiated by a phone call

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from a physician inquiring as to why the original

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infant should have a value of 1.5 and yet have no

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documented evidence of having been given digoxin.

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Q. It was in effect in the

laboratory then that it happened?

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A. Oh, yes, the results were

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reported from the -- actually it was the lab at

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VGH.

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Q. It is perhaps a little bit

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difficult for us as lawyers to have some appreciation

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for the event itself. You say in your letter to

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the editor that -- it spoke of surprise. Was it the

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type of thing where you jump up and down with

excitement shouting "Eureka"?

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A. I guess the element of surprise

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came because previously the highest level that

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had been reported of a digoxin-like substance in

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man typically were less than .2 and the methodologies

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that were used to measure those levels had to be modified to make them even more sensitive than was normally the case. So we were surprised because of the magnitude of the levels that we were seeing. We did not expect anything to be as high as what we were seeing.

Q. Obviously what we have seen in terms of the articles that have been filed by Mr. Lamek, there a number of other parties involved in the same race as you are?

A. That is right.

Q. Is it fair to say it is really a race to try and find out what this thing is?

A. We certainly felt the moment we published that the race would be on because I think that what we are seeing here is maybe a natriuretic factor, some new hormone.

Q. You think it may be some new hormone?

A. Yes, that is the underlying thought at the moment, that maybe this is the postulated natriuretic hormonal factor that people have talked about for years which is basically a substance that would promote the excretion of sodium by the kidney. There has been evidence in lower animals





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suggesting the existence of such a factor.

Q. So this is something that has been theorized for some time?

A. Yes, and some indirect evidence, but always the amount of material that people are able to obtain to work with was always very, very low and the significance of our observation is that in this particular age group it is very high so, from a research point of view, that is a very interesting observation.

Q. So when you mentioned in your evidence that you were stockpiling the serum, what you really had in mind was setting aside the thing you know may find the something?

A. That is right. We have stockpiled as much of the antibody that gives us the highest degree of cross-reactivity that we could obtain from the manufacturer.

Q. If I understand what you said, sir, in the course of your evidence, one of the things you may do in trying to isolate this something is that you may use an HPLC methodology.

A. We have a grant pending, and certainly that forms a major component of the grant.

Q. The use of HPLC?





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A. That is right.

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Q. Are you able to give any

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comment at this stage as to whether HPLC is or is  
5 not likely to isolate this thing?

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A. I think that one has to set

7

up a methodology and determine whether or not it  
8 can or cannot separate the substance from digoxin.

8

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Certainly I think the odds would  
10 favour at this stage that the two compounds would  
11 come out fairly close to each other on highpressure  
12 liquid chromatography, mainly because the antibody  
13 recognizes those species.

13

Q. So it would be fair to say then

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you cannot really say at this point?

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A. No, I cannot say until I have  
16 an opportunity to examine it.

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Q. If I may, I would like to

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17 summarize what I understand to be some of your  
18 findings.

19

Do I understand, first of all, that

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according to your observations this substance is in

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21 the blood of all infants under the age of two months,  
22 to a greater or lesser extent?

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A. Well, we have measured, I guess

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I would have to say in some infants it would be  
25 below the detectible limit as published by the

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manufacturer for the methodology, which is usually  
.2. In some infants we would get a .15, but  
typically most infants do have levels greater than  
.2, in that age group.

Q. May I take it, sir, that you  
have measured not only the 25 that you referred to  
in your article but a good number more than that?

A. Yes.

Q. Can you give us any indication  
of how many infants you or your group have measured?

A. It would be greater than 300,  
I would think.

Q. Greater than 300 separate  
children?

A. Yes.

Q. In that under two month age  
group?

A. Yes, that is where we have been  
focusing our attention.

Q. Do I understand then that in  
all of those 300 infants you have found this X?

A. Yes.

Q. Subject to the levels that you  
mentioned just now?

A. That is right.





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THE COMMISSIONER: You say that you  
did find it in all of them, Doctor?

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THE WITNESS: I guess the question  
really comes down to if you accept the lower limit  
of sensitivity of the methodology to be .2, There  
have been one or two at .15, slightly below that  
cutoff, so if you want to delete those two then you  
would have to say that the vast majority had  
significant levels of the material, except in those  
very few that fell below the .2 level.





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Q. So, when you say the vast majority had significant levels, you're talking about levels in excess of .2?

A. That's correct.

Q. Levels to the extent that you can be satisfied that when it is measured with the method you are in fact measuring X?

A. Measuring a substance, yes. It's a real value.

Q. I'm sorry?

A. It's a real value.

Q. Yes, it is a real value, not background or distortion?

A. Yes, yes.

Q. Do I also understand, and I think it is stated in effect in your letter, that this substance, according to your research, virtually disappears in normal healthy children after the age of 2 months?

A. That's been our experience that it does decrease with age.

Q. And it decreases with age - is it fair to say it virtually disappears? I really do not want to put words in your mouth and I hope you will disagree with me.







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A. Well, the few children that we have done that have been greater than 2 months of age basically were down at the .2 or less level in normal healthy individuals at that age.

Q. And when you say that few children in that age level then, is it fair to say the majority of your research is children under 2 months?

A. Yes.

Q. The next question then is, do I understand correctly that in premature children, babies born before term, I believe term is 42 weeks, is that right?

A. Forty weeks gestation.

Q. Forty weeks?

A. Yes.

Q. Do I understand that in babies born before 40 weeks, the levels tend to be higher than in full term babies, or is that not something --

A. Could you repeat that again?

Q. Yes. Do your findings suggest that in premature babies the levels are higher, generally speaking, than in full term babies?

A. Well, certainly it is within that group that we have found our highest levels.





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Q. And do I take it also that

within that premature group, the duration of the factor being present is longer, in other words, it lasts more than perhaps two months?

A. Yes.

Q. Do I understand, and you made some reference to this in your evidence, do I understand that the health of the child may be a factor in the detection of this substance, or the level of this substance, and let me be as specific as I can. Suppose you are dealing with a child less than 2 months who has a heart condition, let us say congestive heart failure, would you expect that condition to have some effect on the level of X detected in that child, assuming the child isn't on digoxin?

A. Well, we're in the process of investigating that. Obviously it's a very important question to be answered, what are the factors that dictate the levels of X, and I don't have an answer for you on that.

Q. The next conclusion I take it we can draw both from your article and from your evidence is that the levels detected vary obviously from kit to kit?





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A. Correct.

Q. And you have mentioned that you in your testing I think tested at least seven different kits?

A. Yes.

Q. Was one of the kits you tested the Beckman kit?

A. No.

Q. Are you familiar with that kit?

A. I haven't used it but I'm familiar with the Beckman Company, I know they make a kit.

Q. Do you have any information or have you seen reports at all in the literature with respect to variations as they pertain to the Beckman kit?

A. No, I haven't.

Q. Did you notice - I see in this Exhibit No. 9, the article that was in the Journal of Pediatrics which I assume probably has come to you just as recently as it has come to me. This article suggests, if you look at page 949, and specifically the chart that's shown there, I think also it appears in the body of the article itself, a suggestion that the level of this substance may rise for a time after







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birth. Did your research indicate something to that effect?

A. We have a publication submitted that would demonstrate the same observation.

Q. So, what is set out in this report is consistent with your observation?

A. In certain individuals we say see a day to day variation.

Q. Not only a day to day variation, but to be specific, did you detect this rise after birth that seems to be noted in Exhibit 9?

A. In certain individuals, yes.

Q. While you have Exhibit 9 in front of you, I suppose it is fair to say that even though unfortunately the authors of this report didn't see fit to quote or refer to your observations in their report, that basically their conclusions support your conclusion?

A. I think that's fair to say that.

Q. And if you wouldn't mind looking in the headnote, or what I will call as a lawyer the headnote, I don't know what you as a doctor call a headnote, on the very first page in italics at the top.

A. The abstract.





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Q. The abstract, all right. The

last sentence in the abstract says:

"Our results cast considerable  
doubt on the reliability and  
clinical utility of digoxin  
radioimmunoassay measurements on  
the serum or plasma of neonatal  
and infant patients."

I take it from what you have said  
about the therapeutic drug monitoring and monitoring  
of digoxin that you would basically agree with that  
conclusion stated there?

A. Yes.

Q. And if you would look again on  
the first page at the bottom of the left-hand paragraph  
in the main body of the text, the last sentence there  
says:

"The presence of this material in  
plasma ..."

Do you see that?

A. Yes.

Q. "The presence of this material  
in plasma causes false positive  
digoxin values of sufficient magnitude  
to compromise the reliability and





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"clinical utility of digoxin  
measurements in this patient  
population."

I take it that you would agree with  
that as well?

A. Yes.

Q. Doctor, you mentioned in the  
course of your evidence references to research in  
lower animals, I think was your terminology, which  
I believe you indicated supported your conclusions,  
or was consistent with your conclusions. Are you  
able to indicate briefly what that research was or  
is?

A. Well, really, my reference I  
think to the lower species really related to the  
presence of a digoxin-like substance. It was basically  
referring to some early work with a natriuretic  
hormone in rabbits and rats and volume expanded  
animals. These workers were able to isolate an  
endogenous digoxin-like substance, the substance in  
fact had the same effect that digoxin has and that is  
basically to inhibit sodium potassium ATPAs enzyme.  
This material was recognized by digoxin antibody  
methodologies. So, it was in that context that I  
referred to it.







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Q. Are you able to say at this point whether the something that you've identified is the same something that was present in these lower animals?

A. No.

Q. You also indicated in the course of your evidence that some material may be evident in some pathological conditions in adulthood. I think that was the note that I made of it.

A. That's correct.

Q. Can you tell us what you're referring to there?

A. Well, there was an article published in the Annals of Internal Medicine of April of this year.

Q. It's called the Annals of Internal Medicine?

A. Yes.

Q. Yes?

A. I have a copy of the article I think. Here it is. The title of it was "Anomalous Serum Digoxin Concentrations in Uremia". Page 483.

Q. What is uremia?

A. Uremia?

Q. Yes.









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A. Well, this basically refers to impaired renal function.

Q. That's a kidney disease?

A. A kidney problem, kidney failure.

Q. And was there some suggestion that this material was present, or a material similar to X was present in adults with kidney failure?

A. Certainly in the discussion of the paper it was one of the possibilities that the authors raised to account for their observations.

Q. I suppose you're not able to say whether this thing that's been identified by the authors in adults is the same as your X?

A. No.

Q. I suppose with any luck X may become the Seccombe hormone, or whatever?

A. I wouldn't count on it.

Q. I see. On the subject of kidney failure, as a doctor can you tell us, are diuretics one of the things you give to patients with kidney failure?

A. Well, in certain circumstances I think they would be indicated.

Q. And would I be correct in







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understanding that with patients with congestive heart failure that kidney failure is very often a consequence of that?

A. Often it is secondary to poor <sup>er</sup>profusion of the kidney that you can have significant kidney problems.

Q. And one of the things you may do to a patient with congestive heart failure and kidney problems is you give the diuretics?

A. Yes.

Q. Are you able to assist us as to what the effect of diuretics may be in producing this substance X?

A. No.

Q. Is that something you're going to be looking into?

A. Well, I know there are reports of cross-reactivities I think with certain diuretics and digoxin radioimmunoassays. We may get into it but certainly it's not the focus of my attention at the moment.

Q. I take it you can't assist us at this point as to whether or not there is any effect or not?

A. No, I can't help you.





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Q. Doctor, in the course of your evidence, I think pointing up to the problems that may result from the existence of this substance X, you mentioned a child who had been I think admitted to your hospital, or perhaps it was simply a child who had been referred to you where you found that the child was grossly toxic?

A. No, I don't believe I said that.

Q. Do you recall your evidence on that?

A. No.

Q. I had understood that --

A. This was the initial case that led us to the onset?

Q. No, no, it was some time later in the course of your evidence where you were suggesting problems that may develop as a result of the presence of this factor X and perhaps being observed in the course of monitoring and I think you, I don't have my notes right here, but I made a note that you used the expression "grossly toxic" in reference to a particular child who had been referred to you.

A. Well, if that's your recollection.





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It's not mine and it just doesn't come to mind which particular case you would be referring to.

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Q. All right.

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A. There must be a miscommunication there.

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Q. Well, perhaps some other Counsel may have a better recollection of it than I do, or perhaps I can check my notes and ask you at a later time.

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I take it that what you have been measuring in all your tests has been, to crudely put it, blood from children?

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A. Yes.

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Q. Is it serum, is that what it actually is?

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A. Yes.

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Q. And is that what is standardly used or routinely used for the monitoring of digoxin in hospitals?

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A. I think most of them use serum but I think you can use plasma as well.

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Q. Have you done any -- I'm sorry, let me start again. I assume from what you've already said that if we're looking at a particular premature child, and let's not worry about the extent of

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prematurity, but a particularly premature child who is, let us say, less than 2 months of age, according to your findings and the findings of others there is a high probability that we will find this substance X in the blood of that child?

A. That appears to be so, yes.

Q. And in fact it may well be a higher level of substance X than one would find in a child who is not premature?

A. Under certain circumstances, yes.

Q. Are you able to say what those circumstances are, Doctor?

A. No, we are pursuing that right at the moment.

Q. Now, have you done any research with respect to the presence of this substance X in tissues?

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A. Some preliminary experiment.

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Q. And are these tissues from living

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children or from dead children?

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A. Post mortem tissues.

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Q. Post mortem tissues?

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A. Yes.

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Q. And have your studies disclosed

the presence of the substance X in those post mortem  
tissues?

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A. Yes.

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Q. Are you able to give us an

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indication - let me stop. First of all, are those  
tissues taken at the time of an autopsy?

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A. That is correct.

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Q. Within how long after that?

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A. Oh, usually within 12 to 24  
hours I would think.

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Q. Could it be less than 12 hours?

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A. It is unlikely.

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Q. So somewhere in that 12 to 24

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hour range?

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A. Yes.

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Q. Are you able to give us an

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indication of what levels you have found in the  
tissues?

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A. Well, we - I think it would be out of line probably for me really to get into that now. We are actively pursuing that and some of the preliminary data we have is based on an extraction methodology that we now realize was only about 60 per cent efficient as far as the extraction of our material was concerned.

Q. So at least we can take it, sir, that you have found substance X?

A. We have found substance X, yes.

Q. In post mortem tissues?

A. Yes.

Q. And that is using the RIA method?

A. Using the RIA method that gives the highest degree of cross-reactivity to the substance.

Q. And you are reluctant to indicate what those tests are, what those results are because you have not yet perfected your methodology, is that fair?

THE COMMISSIONER: Just to clarify that last answer is this discovery of whatever it was in a child that had not been, not had digoxin administered to it?







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THE WITNESS: Yes, that is right.

MR. STRATHY: Q. And am I correct, Doctor, that you would prefer not to indicate what those results are at this point because you are simply not satisfied that you have perfected your methodology?

A. That is correct. And we haven't done enough yet I think to establish a pattern.

Q. Can you give us some indication of how many you have done?

A. Oh, about eight.

Q. And did you find substance X in the tissue of all those eight children?

A. When expressed in per gram wet weight you have quite a large multiplier added into your final answer because of going to the wet weight or dry weight whichever. Some would be so low that I would have to say it would be non-existent but others were quite, well, within a significant level.

Q. And I take it then assuming you get funding assistance this is something you are going to be carrying on within the next few months?

A. Yes, right at the moment we are





1  
2 actively involved in that particular aspect of the  
3 project.

4 Q. Do you have any indication  
5 at this point as to when it will be that you will  
6 put down tools and start writing articles?

7 A. We do that the minute we  
8 have the answers and we are happy with the answers.  
9 I don't know, it is a function of funding and  
10 available manpower, et cetera. Hopefully though  
11 probably by Christmas we should have something at  
12 least in a pre-publication form.

13 Q. Of the tissue samples that  
14 you have done have you done any sampling of  
15 tissues, let us say a week or 10 days after death?

16 A. No, not taken out of the body  
17 at that time. We have taken samples with, say,  
18 within 12 to 24 hours of death and maintained them  
19 at minus 70 degrees, we have frozen them immediately  
20 in liquid nitrogen and maintained them at minus 70  
21 until we have analyzed them for our substance.

22 Q. Are you in a position to assist  
23 us today as to whether substance X would be present  
24 in tissues taken from let us say an exhumed body of  
25 an infant less than two months old?

A. Never looked at it.





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Q. So you really can't assist us  
at this point?

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A. No.

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Q. One question as to procedure  
at your hospital, Doctor, and I am going to ask you  
to put it in the context of children who are in  
the hospital for treatment of heart related problems  
and who are receiving digoxin on a regular therapeutic  
basis. Is there a system in place in your hospital  
where the digoxin levels of those children are  
monitored on a regular basis?

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A. Well, one point I should make  
clear here that I work at Shaughnessy Hospital and  
Vancouver General Hospital. The Vancouver Shaughnessy  
Hospital site now has two other hospitals on site,  
one is Grace and also the new Children's Hospital  
and we are all joined. The Shaughnessy Hospital  
lab does all of the digoxin testing for Children's  
Hospital, so within Children's Hospital per se I  
have no knowledge as to what goes on there, all I  
know is that the samples are sent to our little  
laboratory for analysis of digoxin levels.

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Q. Are you able to say then how  
frequently the samples are taken for analysis and  
whether it is done on any regular basis for each  
child?







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A. Typically the blood levels are drawn during the initiation phase of the drug treatment and they do one or two levels just to make sure that the infant is within therapeutic range, and then keep a very close eye on renal function. Unless there has been an impairment of renal function they tend not to repeat their levels too frequently.

MR. STRATHY: Mr. Commissioner, if I could just check my notes with reference to that particular child.

THE COMMISSIONER: Yes, certainly. Do you need it now, you can come back in if you want?

MR. STRATHY: I think I can find it, sir. I think I can put it in context and Mr. Marshall has a somewhat similar recall.

Q. You were asked by Mr. Lamek about the significance of your research in two areas, clinically and forensically.

A. Yes.

Q. It was in the context of the clinical that you said it invalidates the therapeutic drug monitoring of digoxin until you can separate digoxin and X?

A. Correct.





1  
2 Q. And then you said, there can  
3 be all kinds of confusion can result as a result of  
4 substance X. You used the example, and unfortunately  
5 I don't have the particulars of the example you gave.  
6 As I recall it was a child who had apparently  
7 appeared to be grossly toxic.

8 A. Oh, yes, now you are refreshing  
9 my mind. That referred to - I referred to an  
10 infant that had been treated with digoxin and the  
11 doctor had sent the blood to the Shaughnessy Hospital  
12 laboratory for analysis and he titrated his drug  
13 based on the results given from the Shaughnessy  
14 Hospital lab which used the clinical assays method-  
15 ology. Then a few days later he wanted a second  
16 level. In the interim the Shaughnessy Hospital  
17 laboratory had run out of the clinical assay kits.  
18 The technician forwarded the sample to Vancouver  
19 General Hospital for analysis, which uses the NML  
20 methodology, and basically we see about a factor of  
21 2 multiplier between the NML and the clinical assay  
22 methodology. Such that the answer that came back  
23 from Vancouver General was twofold greater than what  
24 he had received a few days earlier from the Shaughnessy  
25 Hospital lab. In fact that value would have placed  
this child, I think it was around 6 or 5.4 or





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2 something like that, and it would have placed that  
3 child within a toxic range. So I was just trying  
4 to more or less point out the kind of confusion that  
5 can sometimes happen when you have titrated with one  
6 methodology and then elect to measure at a later  
7 date using a second methodology.

8 Q. And the reason for that  
9 apparently was the variances between the kits?

10 A. Yes, that is correct, the  
11 antibodies ability to recognize I would think X.

12 Q. And my question to you was  
13 going to be, what was the range that was grossly  
14 toxic and you have given it to me I think around  
15 5.4 per cent?

16 A. That is my recollection, it  
17 was in that neighbourhood, whereas prior it was  
18 about one and a half of that on the clinical assay  
19 method.

20 Q. One final question, Doctor.  
21 I am going to ask you simply to assume for the  
22 present purposes that in January of 1982 a group  
23 of children in the neo-natal ward at Sick Children's  
24 Hospital became quite ill, a group in which one  
25 child died and five recovered. Of the five that  
recovered three were found to have digoxin, or







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2 apparently digoxin in their system. They were all  
3 neonates and two were found to have levels in  
4 excess of .5 nanograms per millilitre and one  
5 was found to have levels of up to 1.3 nanograms per  
6 millilitre. I take it that those findings in light  
7 of your findings would not be a particular surprise  
8 to you and might well be consistent with this  
9 substance X being measured.

10 A. Right.

11 THE COMMISSIONER: Excuse me,  
12 were these children who had or had not been treated  
13 with digoxin?

14 MR. STRATHY: Q. No evidence,  
15 Doctor, that these children had been treated with  
16 digoxin?

17 A. Those results would be not  
18 out of line with our observations, it wouldn't have  
19 surprised me.

20 MR. STRATHY: Thank you. Those are  
21 my questions.

22 THE COMMISSIONER: Thank you,  
23 Mr. Strathy.

24 Mr. Marshall?

25 CROSS-EXAMINATION BY MR. MARSHALL:

Q. I don't have very many questions,





1  
2 Doctor. There are a couple of areas that I want to  
3 explore with you, very briefly. Is it part of your  
4 function at the Vancouver General Hospital and at  
5 the Shaughnessy Hospital to engage in a program  
6 of monitoring therapeutic administration of digoxin  
7 before the staff, is that part of the function  
8 of your laboratory?

9 A. Our laboratory provides a  
10 service for the clinical wards for the measurement  
11 or determination determining blood levels of digoxin.

12 Q. So as a result of your experi-  
13 ence you are quite familiar with what would normally  
14 be encountered, or thought to be therapeutic levels  
15 of digoxin in infants on digoxin therapy?

16 A. Well, subsequent to our  
17 observation we have taken an active role in the  
18 literature and I have had no personal experience  
19 directly with what is an appropriate level, but I  
20 have read reports as to what is an accepted level.

21 Q. Is it not part of any of the  
22 work that you are engaged in at the hospital to  
23 have some understanding what therapeutic levels were?

24 A. That is true.

25 Q. And your understanding was what?

A. My understanding certainly as





1  
2 a function of age of the patient, that I believe that  
3 the Children's Hospital are upper end therapeutic  
4 is 3.5 nanograms per ml. Anything beyond that we  
5 would say it is starting to get into the toxic range.

6 Q. That is beyond 3 point -- ?

7 A. 3.5 nanograms per ml.

8 Q. And as a result of the work  
9 that you have carried out recently and that you  
10 have described for us today, you have determined  
11 that there is this substance X, or what perhaps I  
12 guess you call digoxin-like immunoreactive substances.

13 A. Correct.

14 Q. That may produce a reading in  
15 the standard RIA test of up to 4.6.

16 A. 4.1.

17 Q. 4.1. I understand that that  
18 range is a result of analyses carried on, I think  
19 as you have indicated, from several hundred samples  
20 of serum.

21 A. Yes.

22 Q. And that range on the basis of  
23 your research, the upper end is produced by the use  
24 of one kit, NML?

25 A. That is correct.

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Q. And that you have found by the use of some seven kits in total a very wide range in the results of analyses carried out on the same samples?

A. Correct.

Q. Can you help me, please, by advising what, using other kits, the apparent lower end of that range was ascertained to be?

A. Could you repeat that again?

Q. You have indicated to me that using the NML kit you produced the upper end of that range of readings on these many hundreds of samples?

A. Correct.

Q. The lower range where you have positive findings beyond 0.2 nanograms per millilitre, usually considered to be the cutoff point, what is the lower range, referring to your own data?

A. This data has been submitted for publication and I believe the lowest that we -- the study was conducted using 31 samples to cover the full concentration range as determined by the NML methodology, and then we took that grouping of 31 samples and measured them using six other radio-immunoassay kits.





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Q. Yes.

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A. The lowest mean value for that pooling that we obtained was a .19 plus or minus 0.29 to be the standard deviation.

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Q. Does that mean, and you will have to correct me if I am wrong, does mean that using one of the radioimmunoassay kits on the same sample that with the NML kit produced a reading of 4.1, that a reading very close to 0.2 was produced.

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A. That gives you a rough idea of the range, but I think to be fair one would have to say that the mean for the NML methodology was 1.33 plus or minus 1.1 as opposed to the .19 plus or minus 0.29 so that gives you an idea of the variability in the overall mean.

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Q. Perhaps you can explain it for we lay people a little more clearly, then. I understand from what you are saying that some of the assay kits, presumably related to the nature of the antibody employed, are more specific in terms of the identification of digoxin alone than are other assay kits.

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A. I would be more inclined or more capable of recognizing the X component because none of these infants had been given digoxin.





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Q. It works both ways, does it not. NML, which you have retained a stockpile of, is less specific to digoxin than are some of the other kits.

A. I do not think we can conclude that because if I were to take the six or seven kits and went to an adult with normal renal function being treated with digoxin, each of the methods would give me the same answer.

Q. As I understand it, perhaps you can explain this, on the basis of the work that you carried out, you found a consistent relationship as between the results given by all seven methodologies on the same sample, that is to say if, using the NML results you had a finding of X, using one of the other assays, it consistently on other samples was at or about the same percentage in terms of the amount of the digoxinlike substance located, whether it be 25 per cent or 30 per cent and so on, that same proportionate relationship existed throughout your testing, did it not?

A. We find that it is a function again, back to the antibody, because some of the relationships that we have been able to demonstrate on this 31 sample size, there is a direct linear







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3 correlation between the NML antibody and one of  
4 the other kits tested. Yet, in other kits, the  
5 relationship fits more a parabolic model as opposed  
6 to a linear model.

7 Q. What I am trying to understand  
8 is this. You have reported, albeit pre-publication  
9 presently, on the analysis of the same sample or  
10 samples from the same source, widely disparate  
11 readings from the use of several different assay  
12 kits.

13 A. Yes, of substance X.

14 Q. I presume that if you say,  
15 using the NML kit where you have a reading of 4.1  
16 and the child is not on digoxin therapy that you  
17 conclude that there is in fact 4.1 nanograms of  
18 something that is reacting with the antibody?

19 A. Correct.

20 Q. Using the assay kit designed  
21 to determine the presence of digoxin, another kit,  
22 not the NML, you I take it have other results, some  
23 as low as 2-something, between 2 and 3. Is that  
24 the result of your research?

25 A. Well, I guess it is just the  
figures that you have used are -- taking that 30  
sample size that I mentioned, the NML value would





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be 1.3 as opposed to, say, a .19.

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Q. Whatever the difference?

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A. Yes.

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A. Correct.

Q. It seems to me, and you can correct me and I guess you will if I am wrong, it seems to me that the two statements are true: one, that NML is more specific in terms of its ability to detect the presence of the digoxinlike immunoreactive substance, whereas another kit may be more specific in terms of its ability to determine the presence of digoxin, simply because there is a less potential for cross-reactivity with other substances.

Are those two statement not true?

A. I would say that without the background noise in the system, both antibodies have the capability of recognizing digoxin to an equal extent. Once you introduce the variability of substance X into the system then you are correct





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in saying the two antibodies recognize those to  
a different extent.

I do not think you can say because  
the two antibodies recognize X to a different  
extent that you can say that therefore they have  
a different ability to recognize digoxin.

Q. No, but I am saying, and perhaps  
you have misunderstood me, is would not one of those  
kits, the one with the lower cross-reactivity, be  
a more appropriate kit for monitoring digoxin levels  
in children on digoxin therapy?

A. Yes, it would.

Q. It may very well be that those  
kits are equal in their ability to detect and  
quantify the presence of digoxin?

A. Correct.

Q. But the results given one  
assay are not going to be as subject to false  
positive results as is the other.

A. Correct.

Q. In that sense one assay is  
a better assay for determining the presence of  
digoxin than another?

A. In that sense.

Q. In that sense, where in fact







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you are testing for digoxin?

A. In the presence of the possibility of some background substance.

Q. Yes.

Do I understand then also that the determination of these background levels or the relative sensitivity of a particular assay is a relatively easy matter to determine?

A. Basically, yes.

Q. And if we take as a therapeutic level, by that I mean I take it a level that a medical practitioner seeks to attain in the infant -- what did you say, 3.5?

A. That would be the upper end.

Q. Below that, using the NML assay method, where you, having tested a very large sample, obtained readings as high as 4.1, that assuming that this X substance is cumulative in terms of the analytical results, whether it is cumulative in its effect or not, then the most you would expect to find would be, assuming one is not into the toxic ranges or there are no clinical toxic symptoms, would be something in the order of 7.6.

Is that how it acts, in your view?

A. That has been our experience.





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It is limited experience, but they tend to be additive.

Q. So based on your knowledge and understanding of therapeutic levels, the research that you have carried out to date might serve to account for digoxin levels in infants elevated to the region of 7.6, but would not account, in the absence of clinical symptomology of toxicity for findings -- or might probably not, on the basis of your research, account for findings beyond that limit?

A. Given the current state of knowledge, yes.

Q. So they would not certainly account, and let us be somewhat generous, in your opinion without some other explanation, your findings would not account for digoxin levels in children subject to digoxin therapy, therapeutic administration of digoxin, say about ten nanograms per millilitre in serum?

A. Again, given the current state of knowledge, yes.

Q. The Beckman assay kit was, you indicated, was not employed by you in the course of the research that you were carrying out?

A. That is correct.





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Q. I am not sure, in answer to Mr. Strathy, exactly what your response was. Are you at all familiar with that particular methodology or not?

A. I have not used it, no.

Q. I understand that it uses a double antibody?

A. Yes.

Q. Is that a concept or methodology that is at all familiar to you?

A. I have read about it; I am not up on it.

Q. You have not considered whether there would be advantages or disadvantages attendant on a double antibody so far as the radioimmunoassay analysis that have been carried out?

A. No.

Q. You have indicated I think as well when you answered some questions from Mr. Strathy that you would be engaged in the future in attempting to isolate this mysterious substance that reacts to a greater or lesser extent with the various antibodies in these assay kits, and you would propose, I understand, to use a high pressure liquid chromatography methodology in order to







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facilitate that extraction and identification.

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A. Yes.

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Q. Is it your understanding, and

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I presume it is, that that is an appropriate

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methodology to employ, and that your expectation is

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that that methodology would allow you to separate

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out and extract that particular substance for later  
identification?

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A. Certainly from an expediency

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point of view it is the route to go. It is a very rapid

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method. Whether or not it is going to enable us

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to separate our material, we just don't know yet.

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Q. But it is your expectation?

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A. We expect that certainly it

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should be pursued, yes.

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Q. I would hope that you expect

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positive results from that activity?

A. For sure.

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MR. MARSHALL: Yes. I'm not sure I have any other questions. It will be very brief in any event, perhaps it's a convenient time to break now.

MR. LAMEK: Mr. Commissioner, just before we break, and again, to facilitate scheduling if we can, I wonder if other counsel could give me an idea of (a) whether they propose to cross-examine and, if so, what length.

THE COMMISSIONER: Mr. Roland?

MR. ROLAND: I have no questions at this stage.

THE COMMISSIONER: Okay, Mr. Roland. Mr. Rosenberg?

MR. ROSENBERG: Yes, I'm the same.

THE COMMISSIONER: Ms. Goodman?

MS. GOODMAN: I have no questions, thank you.

THE COMMISSIONER: Ms. Symes?

MS. SYMES: I have no questions, thank you.

THE COMMISSIONER: Mr. Young?

MR. YOUNG: I am not proposing to cross-examine.

THE COMMISSIONER: Mr. Ortved?





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MR. ORTVED: Very brief.

MR. LAMEK: I'm sorry? What did Mr.  
Ortved say?

MR. MANNING: He said very briefly if  
at all.

MR. LAMEK: Thank you.

THE COMMISSIONER: Mr. Manning?

MR. MANNING: Five to ten minutes.

THE COMMISSIONER: Mr. Tobias?

MR. TOBIAS: I would think no more  
than 10 minutes, Mr. Commissioner.

THE COMMISSIONER: Well, it looks  
as though we might come to another witness this  
afternoon. Is there one available?

MR. LAMEK: Yes, I think there may be.

THE COMMISSIONER: Yes, all right.

MR. LAMEK: Thank you.

--- Luncheon recess.







AA/BB/ak

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2 ---Upon resuming at 2:30 p.m.

3 THE COMMISSIONER: Mr. Marshall?

4 MR. MARSHALL: A couple of short  
5 questions and I will be through, Doctor.

6 CROSS-EXAMINATION BY MR. MARSHALL: (Continued)

7 Q. Were any of the RIA kits that  
8 you've used double antibody kits?

9 A. No.

10 Q. Now, you were asked some  
11 questions about some research that you had engaged  
12 in involving post mortem tissue. Do I understand  
13 your response to those questions that, or by your  
14 response to those questions, that because of the  
15 methodology used and so on, it would be difficult  
16 for you to address any particular significance to  
17 be given to those particular results at this time?

18 A. Well, let's say we are currently  
19 investigating tissue levels of our substance X  
20 that during the course of these investigations there  
21 were some methodological considerations that had to  
22 be worked out, that our preliminary data was based  
23 on an extraction method that we subsequently have  
24 determined to be less efficient than another one that  
25 we've now developed. So that I think for me to  
give you levels, tissue levels based on an extraction





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2 methodology that we find is less efficient than  
3 what we can now currently use would be misleading  
4 and it is preliminary data anyway, so, we are  
5 going to carry on and as soon as we have the figures  
6 we publish them.

7 Q. How long has that work been  
8 going on?

9 A. Basically it's been going on  
10 for about five months.

11 Q. On what kinds of tissue?

12 A. We have extracted heart, liver,  
13 kidney, gut. We haven't done skeletal muscle, but  
14 certainly a wide range of tissues. We've also  
15 looked at blood drawn from different portions of  
16 the body to see whether or not we can isolate the  
17 origin of our material.

18 Q. On a large number of individuals?

19 A. Not on a large, I would say  
20 approximately eight at the most.

21 Q. I'm sorry?

22 A. Approximately eight.

23 Q. And these are infants?

24 A. These are infants, some very  
25 premature infants that died, none of whom had ever  
been given digoxin.





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Q. Well, when you say of the eight, some of whom - would the majority of them be - how many of them would be premature babies who died, for instance?

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A. I would have to go back and look in that data for you to give you that answer. I just cannot remember. In the early stages we were taking basically any autopsy material we could get a hold of and there wasn't much direction given to the pathologist as to specific age groups. So, we were extracting older children, children that died, that were one and a half years of age, for instance.

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As we narrowed in on this problem a little more completely, we then focused our attention to low weight premature infants.

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Q. And the objective of that research primarily was what?

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A. Is to basically, number one, determine relative tissue concentrations of our substance X.

Q. I'm sorry, relative to what?

A. Relative from tissue to tissue.

Q. Within a single individual?

A. Yes.







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Q. And I take it that that is  
something in the future?

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A. That's right.

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Q. Yes. What else?

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A. And hopefully gain some insight  
as to either the origin of this substance and/or  
the primary target organ for the substance, if in  
fact there turns out to be one.

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Q. Specimens that you utilize,  
I gather from what you were saying, were not procured  
in what I might refer to as a particularly scientific  
manner in terms of ensuring that particular organs  
of choice or specimens from organs of choice or  
specimens from organs of choice were obtained,  
I take it you took what was available, is that  
correct?

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A. The pathologist on removing  
the tissue at the time of autopsy immediately placed  
it into liquid nitrogen and the tissues were kept  
at minus 70 degrees until we extracted them at  
some later date.

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Q. And I take it you are hesitant  
about discussing any results of those testings with  
us?

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A. I think at this stage it would





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be -- yes, I'm hesitant. It is premature at this stage.

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Q. You would rather not?

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A. Yes, that is correct.

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Q. Thank you very much.

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THE COMMISSIONER: Thank you.

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Yes, Mr. Roland?

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MR. ROLAND: Yes, a question or two.

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CROSS-EXAMINATION BY MR. ROLAND:

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Q. It is a question that arises out of Mr. Marshall's questions of you about the double antibody RIA procedure. Exhibit 10, which was put in this morning, which is the study done by Brett, which I think you had been referred to by Mr. Lamek before you testified, it seems to me to indicate, that at least as far as that study is concerned, the one double antibody, RIA procedure gave a higher false positive result than the single antibody RIA procedures. Am I correct in my reading of that?

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A. I guess the statement in the abstract is that one double antibody RIA procedure gave false positive results.

Q. Yes.





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A. In 95 per cent of the infants.

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Q. Which seems to be higher than the false antibody results for the other single RIA procedures?

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A. As reported in this abstract, that seems to be.

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Q. I'm understanding the abstract correctly then, am I?

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A. Having a look at it, I would classify this as an abstract of some preliminary work that's gone on and the initial observations as found are listed in this abstract.

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Q. Yes. And this abstract indicates that there seems to be a higher degree of false positive results with the one double antibody procedure that they used then with respect to the single antibody procedures.

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A. Yes, if you assume that both our procedures that were used in measuring the same samples, yes.

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Q. Yes, all right. Is there any reason why you didn't choose a double antibody procedure?

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A. Well, we didn't - I guess basically the one we were using was a single antibody.

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I think that of the procedures used in North America,  
3 the vast majority of them tend to be single anti-  
4 body methods.

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Q. Yes.

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A. And also we had more experience  
7 with the single antibody method.

7

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Q. Yes. Thank you. Those are  
8 all the questions I have.

9

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THE COMMISSIONER: Yes, thank you.  
10 Mr. Rosenberg?

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MR. ROSENBERG: No questions, thank  
12 you.

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THE COMMISSIONER: Miss Goodman?

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MS. GOODMAN: Yes, thank you.

15

CROSS-EXAMINATION BY MS. GOODMAN:

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Q. Dr. Seccombe, you indicated  
16 that you have some limited experience with the  
17 detection of substance X in serum for infants who  
18 were not on digoxin therapy and who were later  
19 administered digoxin.

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A. We have run into that experience,  
21 yes.

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Q. And how many such cases have  
22 you studied?

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A. I would think two or three.





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Q. And what were the levels obtained before and after the administration of digoxin?

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A. I would have to go back to be completely accurate to refresh my memory, but basically the conclusion that we initially received from the data was that the administration of digoxin was additive to the result that we had obtained prior to the digoxin. So, in other words, if you had a base line of one and were targeting for a 3 with your dose of digoxin, you would end up with something higher than 3.

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Q. Do you recollect if any of those final results were above what I believe you said was the upper end of the therapeutic level, which would be 3.5?

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THE COMMISSIONER: That's the normal. I mean, 3.5, is that the upper end?

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THE WITNESS: That is the normal cut-off for the upper end, yes.

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THE COMMISSIONER: Is it?

THE WITNESS: Yes. It varies but it is in that range, 3.5.

You see, it is a function of which particular antibody we were using at the time of





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2 the methodology and we discussed prior to lunch that  
3 one individual case where we were following that  
4 individual and it was given that the two methodologies,  
5 there was quite a discrepancy between the answers.  
6 The one inference that I'm talking about now, the  
7 method that we were using for that infant was the  
8 clinical assays method which has about approximately  
9 one half the degree of cross-reactivity of the NML  
10 method. When we treated it with digoxin, the baby  
11 went to the upper end of the therapeutic range but  
12 didn't exceed it.

12 MS. GOODMAN: Q. Didn't exceed it.  
13 And what were the ages of the children involved in  
14 those particular cases?

15 A. I'm just wondering if I have  
16 the data with me on that kiddie. I can't lay my  
17 hands on it right at the moment but it was a pre-  
18 mature infant, approximately 10 to 11 days of age.

19 Q. In other words, of the few  
20 that you have referred to would be within the  
21 two month range?

22 A. That's true, less than two  
23 months.

24 Q. And with respect to their  
25 health, they would have either been premature or







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they would have been infants?

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A. Correct?

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Q. Thank you. And you stated also

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that your research to date might serve to account

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for an elevation up to 7.6, and I take it from that

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you meant the 4.1 being the highest level that you

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have reached to date in measurement of substance X,

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plus the high range of therapeutic level of 3.5?

A. Yes.

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Q. And with that 7.6, would a

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reading of 7.6 on a child who had been on digoxin

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therapy, would you expect toxic effect?

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A. Well, it would all depend on

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whether or not the substance X has biological

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activity similar to digoxin.

Q. And can you speculate on that?

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A. Not at the moment. We have

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some preliminary evidence but that's premature.

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Q. That preliminary evidence

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indicates?

A. It falls into the same realm

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as the tissues. We are pursuing that very actively

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at the moment, I think that is a very real and

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important question that has to be answered.

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Q. Thank you.

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THE COMMISSIONER: Thank you,  
Miss Goodman.

Miss Symes?

MS. SYMES: No questions.

THE COMMISSIONER: Mr. Young?

MR. YOUNG: No questions.

THE COMMISSIONER: Mr. Ortved?

CROSS-EXAMINATION BY MR. ORTVED:

Q. I take it that what you have  
been telling us today, Dr. Seccombe, is that your  
study is really very much in its infancy, would that  
be fair?

A. That's a fair statement.

Q. And I take it that might be  
extended to the study of some of the aspects of  
digoxin generally, as Mr. Lamek has already indicated,  
correct?

A. That is correct.

Q. As well as your study being in  
its very embryonic stage, as I take it you will  
agree with me, that the sample certainly upon which  
you have reported here today is a very small one.

A. As it relates to the blood  
levels I would say that it is certainly from a  
scientific point of view a significant number. As





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far as tissue levels are concerned, I would agree with  
your statement.

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Q. Well, in terms of blood levels  
and your characterization of significant number,  
we are talking about in terms of what, 35 or 40.

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A. Since the initial observation  
was made we have done well over, well, I would say  
in the neighbourhood of some 300 samples.

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THE COMMISSIONER: I'm sorry, 300?

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THE WITNESS: 300 samples.

MR. ORTVED: Q. In terms of what  
you have reported upon to us, we are really only  
talking of a sample of something like 25, plus  
another 10, isn't that correct?

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A. We're talking in the initial  
published letter to the editor in New England, a  
sample size there of 25.

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Q. Right.

A. The current publication that's  
submitted represents - there's an end value of that  
size 31, but in our session I pointed out that  
because of the limitations of sample volume that  
there had to be a lot of analyses done prior to  
carrying out that investigation in order to pull  
up appropriate levels of samples that had X in it.







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Q. Right.

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A. So that we could carry out  
our further studies.

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Q. Okay. My point is that you  
haven't really reported to us on the samples that  
are the subject matter of your second paper. You  
really are only reporting to us today on your first  
paper, right?

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A. Yes, I guess that's it, yes.

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Q. Because, really, we haven't  
questioned you about the subject matter of your  
second paper because we don't want to impair the  
aspects of its publication.

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A. Yes, it is pre-publication data,  
that's right.

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Q. That's right. In terms of the  
actual sample that you've been questioned about today,  
that's a small sample?

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A. That's a small sample.

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Q. And even if we were to talk in  
terms, Dr. Seccombe, of a sample of 300.

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A. Yes.

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Q. Am I correct in understanding  
that various of these scientific investigations  
involve thousands upon thousands of samples?

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A. Yes, obviously the more times you can make an observation the more significant it is and it is comforting to see that many other people are making the same observations.

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Q. And then I take it that you would agree obviously that we know a lot more about digoxin and aspects of digoxin and in terms of levels of digoxin and what is and is not a possible false positive in 1983 than was the case for instance even a year or so ago.

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A. I think that's a fair statement.

Q. And you've told us that based upon your analysis, the ultimate effect of your false positives, if in fact digoxin is administered, is an additive effect?

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A. That's correct.

Q. And you've told us about the various elements which can operate to vary these false positives, I won't repeat those, but I think to summarize something you've said, certainly age is one item which, in your investigation, affects these false positives?

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A. That's correct.

Q. On the other hand, you've told us about a publication that suggests, although





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2 your false positive would appear to be confined  
3 for the most part to neonates and premature children,  
4 there is at least one writer who is hypothesizing  
5 that this may also be the case in adults, is that  
6 correct?

7 A. That's correct.

8 Q. So, there may be additional  
9 ramifications of these investigations that we don't  
10 know about yet.

11 A. That's for certain.

12 Q. And furthermore, you mentioned  
13 that one of the factors that can't be discounted  
14 in terms of variation is illness?

15 A. Correct.

16 Q. And I don't know whether you  
17 were questioned about this, but I take it that one  
18 of the categories of illness that we have to  
19 consider is possible congenital cardiac effects.

20 A. Certainly it would have to be  
21 considered.

22 Q. But, as I understand the sample upon  
23 which you have conducted your investigation upon which  
24 you reported today, it was not, it did not include  
25 or was not confined to patients having congenital  
cardiac defects.

A. There were some infants







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within that group that had cardiac congenital

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defects but certainly it wasn't confined to that

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population.

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Q. Right. And as far as you are

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aware, I take it that there is not presently

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available a study which would pursue those questions

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which you have been pursuing in relation to

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congenitally cardiac deformed babies exclusively?

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A. Not to my knowledge.

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A. Not to my knowledge.

Q. But again I take it it is one of those questions that has to be raised?

A. Certainly.

Q. I think what you are telling us is that the potential additive effect of what may be an endogenous substance in congenitally cardiac deformed babies is not known?

A. No.

MR. ORTVED: Thank you. Those are my questions.

THE COMMISSIONER: Thank you, Mr. Ortved. Ms. Solomons?

MS. SOLOMONS: No questions.

THE COMMISSIONER: Mr. Olah?

CROSS-EXAMINATION BY MR. OLAH:

Q. Doctor, just a couple of things I would like to clear up with you. In these preliminary tissue studies that you have done did you find that there was a variation of concentration of this "X" substance depending on what kind of tissue you were sampling?

A. Well, we were seeing some variation, yes.

Q. For example, and let me see if





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I can help you. Did you find that the concentration of this substance was higher in heart tissue plus the atrium than in accordance with other tissue?

A. Well, as I say we found variation between tissues but the variation I must say was based on an extraction efficiency that was sub-optimal and it is very difficult-and very small sample size, I can say we were finding tissue variations. So I think it is really preliminary to sort of go out on a limb and say we found more in the heart than elsewhere.

Q. All right, given the fact, or the appearance that the chemical qualities of this substance seem to be very similar to digoxin, is it probable, as in the case of digoxin, that you are going to have a higher concentration of Substance X in the heart than in other areas?

A. Well, certainly if you look at the distribution of digoxin in tissues there seems to be a tissue to tissue variation and that is based on the degree of binding of the drug to protein in the tissue. In the case of our Substance X, if you say it is similar in structure to digoxin then you have to expect the same sort of parallel, I would think.







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Q. And your preliminary observations, have they borne out that hypothesis?

A. As I say, I think it is premature to take a jump there.

Q. The other factor I was interested in is, I believe there is some literature that I believe suggests there is a multiplier effect between pre mortem digoxin and post mortem digoxin levels of blood. Are you aware of those studies?

A. Yes.

THE COMMISSIONER: I am sorry, what was that?

MR. OLAH: Q. There is a multiplier effect, Mr. Commissioner, between pre mortem blood and post mortem blood. Do you have any data, or is there any literature that would suggest that this kind of a multiplier effect relates also to this Substance X?

A. We have seen that multiplier effect in one infant, but unfortunately the infant had been treated with digoxin. We had followed the infant longitudinally for several days and about 12 hours prior to its death it was given a loaded dose of digoxin. At the time of death there was an intra-cardiac heart puncture done and a blood sample was







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taken and then the following morning at autopsy a second blood sample was taken, and within the interim we saw an elevation of about 1 to 1-1/2 nanograms per ml. That is the only one we have looked at. I haven't looked at it as it relates specifically to our Substance X, that study obviously was contaminated with digoxin so we don't know whether it was digoxin or "X" that we were seeing.

Q. Did you anticipate the same kind of multiplier factor to apply to the substance as in the case of digoxin?

A. Well, if you want to follow your same, your original argument that the "X" is similar in structure to digoxin at some level and binds to the same degree, then until proved otherwise I guess you would have to say the odds would favour it.

Q. When you were being examined by Mr. Strathy he asked you about the results of Exhibit 9 which concluded that there must be considerable doubt as to the reliability and clinical utility of digoxin RIA measurements on serum or plasma?

A. Is this the Brett Paper?

Q. This is the Valdes Paper.

A. Yes.





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Q. Would you suggest that the same kind of caution must be exercised when one is approaching tissue samples?

A. I would say, yes.

Q. And one final area that intrigued me, is high pressure liquid chromatography. If one didn't know or wasn't looking for Substance X and one thought they were obtaining only digoxin, is it likely that this Substance X would be contained in that ultimate residue that is left over?

A. Well, I think certainly my experience with high pressure liquid chromatography indicates that the more similar two compounds are in structure the greater the likelihood is that they will come off the column very close to each other, if not on top of each other. So it all depends on how different in structure Substance X is from digoxin. If it is very different, if they were to separate quite nicely I would anticipate, and if they are very similar with very small differences say on a ring structure involving one weighting of some sort then I think the odds are fairly good they are going to come off fairly close to each other.

Q. Do we know whether the fingerprints of these two drugs, if I may call them that,





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are quite different or overlapping, or is there any evidence to that effect?

A. I don't have any evidence to that effect. All we know is that the antibodies that are supposedly specific for recognizing digoxin recognizes some other substance and has difficulty in separating that other substance from digoxin. So I have to assume until proved otherwise that other substance is very similar in some respects to digoxin.

MR. OLAH: Thank you very much, Doctor. Thank you, Mr. Commissioner.

THE COMMISSIONER: Thank you, Mr. Olah. Mr. Shanahan?

MR. SHANAHAN: I have no questions.

THE COMMISSIONER: Mr. Manning?

CROSS-EXAMINATION BY MR. MANNING:

Q. Doctor, I notice in your Curriculum Vitae you got a Ph.D. in 1981 and an M.D. in 1981, is that correct?

A. That is correct.

Q. Did you get your Medical Degree through the University of Calgary after studying at the same time for your Doctorate of Physiology?

A. I started my Doctorate studies prior to going to Medical School, I enrolled in







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Medical School and finished writing my thesis during

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Medical School and defended the thesis at the time

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of graduation from Medical School.

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Q. In the list of abstracts at

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page 2 of your Curriculum Vitae, Item No. 8.

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A. I am not even sure if I have

a copy, I have it, yes.

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Q. You have listed a paper

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co-authored with other persons?

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A. Correct.

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Q. That has been, and this says:

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"Accepted for presentation at Joint Congress on

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Clinical Chemistry, Quebec, June 1983".

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A. That's correct.

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Q. Is that the as yet unpublished

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document that you have been referring to in your  
testimony?

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A. No, it is not. The document,

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the unpublished document that I have is an elaboration

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of that particular abstract.

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Q. So we have, so that I keep

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this straight, the letter to the Editor of the New  
England Journal of Medicine?

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A. Correct.

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Q. Which is your observations and

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conclusions by yourself and your colleagues with  
respect to a study done on 10 out of - on 25 infants?

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A. That is correct.

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Q. That is the 10 out of 25 that  
is reported there?

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A. 10, 10 are reported there,  
10 of the 25.

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Q. Of the 25?

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A. That is correct.

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Q. Now, the second study that I  
have in my mind, which you may have done at a later  
stage is the 31?

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A. Yes, that is the study that  
involves the different kit or methodology comparisons,  
commercial comparisons involving 31 samples.

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Q. Did you write up that  
particular study?

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A. Did I write it up?

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Q. You along with your colleagues?

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A. That is correct.

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Q. Is that published somewhere?

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A. That has been submitted for  
publication and is currently under review.

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Q. And that is not the letter to  
the editor, and that is not Item 8 in your Curriculum  
Vitae?

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A. That is correct.

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Q. Nor is it the expanded version

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of what is to be presented as a paper which is the  
expanded version of Item 8?

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A. No, the paper is an expanded

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version of Item 8.

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Q. Of Item 8. So the examination

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of the 31, if I can call it that for brevity's sake,

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is a fourth paper that has been submitted for

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publication?

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A. There is the letter to the

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Editor of the New England Journal.

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Q. Right.

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A. That was one. There is an

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abstract which is being given at this conference in  
June.

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Q. That is Item 8?

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A. That is Item 8. Then there

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is an article that elaborates ---

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THE COMMISSIONER: Just a moment, it  
is June, we are pretty nearly through June.

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THE WITNESS: Well, in fact I think  
Dr. Pudek is probably giving that paper almost now.

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MR. MANNING: Q. So that paper ---

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A. So there are three publications

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basically, one abstract, a letter to the editor and one that has been submitted for publication currently under review and hopefully will be published.

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Q. And so this abstract will be available for us to read as soon as it is delivered?

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A. Yes. In fact, I am sorry I don't have one with me.

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Q. But it could be released today or at some time in the near future?

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A. Yes.

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Q. Perhaps you would be good enough to give that to Mr. Lamek and then we can have it available for us to look at.

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A. All right.

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Q. And when do you anticipate the paper upon which this abstract was based will be available for publication?

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A. The paper was submitted approximately four weeks ago and it really is a case of the review process and I would estimate eight to twelve weeks.

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Q. Now, turning back for a moment to your letter to the Editor of the New England Journal of Medicine. In that particular letter - do you have it?

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A. Unfortunately I have everything stapled together and it has all come apart, but yes, I do have it.

Q. In that particular letter, in the second paragraph where you state:

"Our observations suggest that an endogenous substance present in the circulation of premature and full-term babies cross-reacts with antibodies to digoxin."

A. Yes.

Q. You used the words "suggest than an endogenous substance ...".

A. Correct.

Q. You were not ruling out, were you, the possibility that there was not an endogenous substance that was present, but some other substance?

A. Well, I guess the statement was phrased in that particular manner to cover for the possibilities that there was some matrix effect or something going on with the samples that would affect the radioimmunoassay per se.

Q. I notice that in the other materials that we were given copies of this morning, for example in what has been marked as Exhibit 10,





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the abstract from the Brett article?

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A. Yes.

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Q. In the last paragraph refers

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to the cause of the current results, they don't call

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them endogenous substances, they call them aberrant  
results.

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A. Yes.

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Q. "... and have tried to

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relate them to low serum protein or

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albumin, high triglyceride or

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cholesterol concentration or to the

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administration of parenteral nutrition;

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but the results have been inconclusive."?

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A. Yes.

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Q. Have you attempted to determine or relate, I should say, these results, these kind of aberrant results or indogenous results as you have suggested in your paper to those factors?

A. Initially we screened the samples in that for certain things, not the protein, not these ones that are listed here but bilirubin is one for instance that they wanted to rule out, and a few things like that.

Then we found out that we could extract the material out of the sample and that led us away from an indogenous interference more into, in fact, a substance that we were dealing with.

Q. The substances that you have looked at, you have not compared the results or seen or attempted to ascertain the effect of other hormones such as testosterone or progesterone.

A. Not ourselves, no. The companies often do analyze their kits for that particular problem.

Q. Is there a reason for that?

A. You can get false positives if the levels become very high.

Q. Knowing that, Doctor, is there any reason why you and your colleagues, in carrying







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out your tests, did not test for that kind of  
reaction?

A. I guess initially when one is  
pursuing something these are issues that one has  
to whittle away slowly. You make the observation  
and then there is always that element of doubt and  
you try and deal with each of your concerns one at  
a time, and we have not come to those as of yet.

Q. In your letter to the editor,  
turning back to it for a moment, on the second page  
you have made reference to a number of patients,  
that is ten, and under the column, medication, it would  
appear -- it does appear that some of the patients  
were on medication of some kind and others were not.

A. That is correct.

Q. Have you had an opportunity  
to date to study the effect of ampicillin or  
gentamicin or any of the other drugs listed  
therein, on the effect of the readings?

A. Initially with this 25 sample  
size we looked for correlation with medications,  
birthweight Apgar scores, and we were unable to  
indentify any correlations between whether or not  
the baby had been given drugs, or Apgar score, that  
sort of thing. But it was a small sample size so





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it is very difficult to draw any conclusions at this stage, I think.

Q. Will you be looking in your larger studies to determine whether drugs such as ampicillin have an effect on the digoxin reading levels?

A. Certainly that is something that has to be done.

Q. Because they may or may not affect the readings.

A. I think subsequent to this, the thing that shied us away from pursuing that line of investigation at the moment is the fact that we were able to achieve a relatively high level, and we see considerable variation of levels within individuals that are on no medication, so I guess if you are saying correlation between level and medication then you would be more actively pursuing the medication story, but because of the fact that babies on no medication can show wide variations in the level of X, we shied away from pursuing that.

Q. Do you know whether the mothers of these babies listed in this table were on any medication such as ampicillin?





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A. I would have to go back and check our records on that, something that we looked into. Obviously, we were depending on the time of birth and the age, in sampling. Certainly, the cord blood samples, we knew that the mother was not on any medication. Those were from healthy, full-term deliveries, except for the breech delivery there. The mom was not on any known medications.

The other infants, if they were within a few days of birth, we would check the records to make sure that the mother had not been treated with drugs. Babies that were older and had been in the nursery for a longer period of time, that precaution was not taken.

Q. Do you know whether any of these mothers had congenital heart problems themselves or indeed later developed heart problems?

A. I do not know.

Q. You indicated just a little while ago that some infants that you had studied had congenital heart defects. Were you referring to the infants listed in this table?

A. I believe there is one there with PDA (inaudible) ductus arteriosus, premature infants I think that is the only other one. That is the







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only other one we have listed in this table. There are one or two others, though.

Q. Have you recorded in the material, the background material which lead up to your Table 1, how the blood samples were taken, that is, whether they were taken from a vein or elsewhere?

A. The samples were all taken from the baby by Dr. Whitfield.

Q. So his records would indicate how they were obtained and from where?

A. That is right. They were all obtained within a very short period of time.

Q. In coming to the conclusion or the tentative conclusion or the suggestion that perhaps this X substance as it has been referred to, or the interferent as it has been referred to in other papers was indogenous, had you studied medical literature or other literature to see what other bodily substances were manufactured indogenously?

A. Certainly after we made the initial observation I began to collect references on digoxin and related materials, natriuretic factor, natriuretic hormone, cardiotropic agents, et cetera, et cetera, and certainly it is not an exhaustive search but I have made some inroads.







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There are other reported findings of digoxinlike substances present in man and lower species as well.

Q. You indicated, or you used the phrase, "the pool-up of levels", I believe in answer to -- in partial answer to some question --

A. Could you phrase that again for me?

Q. Pool-up of levels, the pooling-up procedures that you followed?

A. Oh, yes.

Q. Could you explain to the Commissioner what that means and what procedure was followed with respect to obtaining of these levels.

A. Well, there was no pooling involved at all in the letter to the New England Journal. That was one sample drawn from one infant and run in duplicate on both assays. The pooling came into play when we attempted to assess the degree of cross-reactivity with seven different kits, and this is in a publication that is pending. Basically we analyzed many, many babies that had not been given digoxin and analyzed them using the NML methodology which had the highest degree of cross-reactivity for substance X. Then, based on the answers obtained with that preliminary screen,





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samples were then pooled according to the NML methodology in order to give a pool of .5, .7 to cover the full concentration range of substance X such that we had an end value of 31 and sufficient quantities of the material to carry out a kit to kit comparison.

Q. But that pooling effect would not take into account, would it, the drawing of blood from different parts of different infants' bodies.

A. Basically all of the samples were pooled from routinely submitted blood samples for other chemistries in the main chemistry lab, so there might be some variation as to where the blood sample may have been drawn on the infant but that does not take into consideration that variation.

Q. Coming back just briefly for a moment to the mothers of these ten infants, do your records or would your colleague's records indicate whether any of the mothers were on any diuretics at the end of their pregnancy?

A. Certainly we could find out that information.

Q. Would you agree, Doctor, that when one was going to attempt to find the digoxin





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level that it would be scientifically proper for one to utilize the HPLC test and RIA test, to utilize both tests?

A. In order to --

Q. In order to try to come to as accurate a conclusion as possible?

A. Well, certainly the highpressure liquid chromatography, once having established that you can reliably separate X from digoxin, I would say yes. It is a very powerful technique for not only looking at digoxin but related metabolites.

Q. Suppose the HPLC test were used to separate out digoxin and digoxinlike substances and you could not tell the difference and then you used the RIA test in order to determine whether you had a digoxin level of some kind?

A. Then you have a problem.

Q. A problem?

A. I would think.

Q. In what way?

A. If your high pressure liquid chromatography could not separate the digoxinlike substance from dogoxin itself and your antibody recognizes both species then you cannot quantify them separately.







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Q. What if you did the RIA test first and then did the HPLC test, in the reverse order?

A. If you did the IRA, and given that the antibody recognizes both species you may have a value of 100. Then if you put your material extracted with appropriate standards, internal standards et cetera, and injected it onto your HPLC, you may get a lovely peak that would come off in the area that you would expect digoxin to come off in. But until you are certain that that is all that is coming off in that area then I think you have a problem. You have to be able to discern whether or not you have a contaminating species within that peak.

Q. Have you at any time up until today been made aware of the kinds of tests done on the samples given to the Centre for Forensic Science in respect to this particular case?

A. I have no specific details. It is just what I have read in the press.

Q. Do you know whether from Exhibit 9, 10 and 11, whether the authors of those reports did HPLC tests?

A. I don't know that.





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Q. Can you give us --

A. I might add, though, that if they had I am quite sure they would have documented it in their publication.

Q. Can you give us your own definition as used in your letter to the editor of what you mean by premature? Is there a cutoff number of weeks, is it 35 or 36 or --

A. I would have to look that exact definition up. That was given to us by Dr. Whitfield who is a pediatric neonatologist.

Q. Have you attempted to date to do any research on what has been called the X substance after death, that is, whether the substance breaks down and if so, how long after death; whether it leaves tissue?

A. We have not, no.

Q. Is that your intention to make that part of your study?

A. Oh, yes, that is part of our -- as I mentioned earlier we are pursuing tissue levels of our material and certainly that part of that pursuit involves doing blood levels at the time of autopsy.





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Q. Dealing with the post mortem tissue taken at an autopsy, I believe you indicated that the tissue had been extracted and then frozen and then tests were done?

A. No, the tissue was dropped into liquid nitrogen in total. So, in other words, there was no preliminary extraction, it was just a piece of tissue rapidly frozen.

Q. And that tissue was left frozen for how long before testing?

A. Oh, it varied. I know in the initial phases they were probably extracted within a week of the autopsy. Other tissues have been in the freezer at minus 70 for longer periods of time. But that's something we obviously have to document is what happens to X with time and storage and these are all the questions that one has to do during the methodology development.

Q. In the paper dropped on my desk at noon, and I don't know whether this has been entered as an exhibit as yet.

MR. LAMEK: I don't know what it is.

MR. MANNING: "Anomalous Serum Digoxin Concentrations in Uremia" by Kraver and Valdez.

THE WITNESS: This was a letter that I







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alluded to prior to lunch and gave the reference for  
it to one of the other cross-examining lawyers.

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MR. MANNING: Q. All right. Do you  
have a copy of that in front of you?

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A. I probably do.

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THE COMMISSIONER: Can we make that an  
exhibit?

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MR. LAMEK: I have no objections to  
it, Mr. Commissioner.

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THE COMMISSIONER: No, but it's not  
yet an exhibit?

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MR. LAMEK: It is not yet as far as I  
know.

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THE COMMISSIONER: No. Well, I will  
leave it up to Mr. Manning. Do you want it to be an  
exhibit?

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MR. MANNING: Yes, I think it should  
be an exhibit.

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THE COMMISSIONER: All right. Well  
then, what number are we at?

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MR. MANNING: I believe that's number  
12.

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THE COMMISSIONER: Number 12. Can  
you describe it again?

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MR. MANNING: It's a two page document







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from the Annals of Internal Medicine.

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THE COMMISSIONER: Oh, yes, I remember that.

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MR. MANNING: Volume 98, No. 4, April, 1983 page 483 entitled "Anomalous Serum Digoxin Concentrations in Uremia" by Kraver and Valdez.

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--- EXHIBIT NO. 12: Document entitled:  
"Anomalous Serum Digoxin Concentrations in Uremia"  
by Kraver and Valdez.

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MR. MANNING: Q. I notice, Doctor, from a brief reading, quick reading of that particular document that on the front page in the second paragraph where there is a description of the individual, the individual the case report is about, there's a reference to digoxin therapy. This is about a third of the way into that indented paragraph.

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A. Yes.

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Q. "Digoxin therapy was withdrawn when he developed renal failure caused by post operative intra-vascular fluid depletion and possible toxicity from long courses of tobramycin treatment."

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Have you been made aware through your studies, through your research of the literature, of the effect of tobramycin on digoxin levels of readings?

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A. I think the tobramycin toxicity probably relates to its effect on the kidney.

Q. I see.

THE COMMISSIONER: I'm sorry, relates to what?

THE WITNESS: Its effect on the kidney.

THE COMMISSIONER: Oh, I see.

THE WITNESS: That the drug can be toxic to the kidney and they are postulating that that's why this gentleman went into renal failure.

MR. MANNING: Q. I see. But I notice also, just --

A. And the sequence to that then would be if tobramycin is nephrotoxic or toxic to the kidney. The general of thinking at the moment is the kidney is a primary organ for elimination of digoxin so, therefore, malfunctioning kidneys would obviously affect the metabolism of digoxin or its rate of elimination from the bloodstream.

Q. Which would result in a higher reading?

A. Yes.

Q. Well, actually, would it result in a higher reading or would it result in the actual reading in the blood at the time before the material





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could be even metabolized?

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A. I think that what would happen with a gradual decline in renal function that there would be a gradual increase in blood levels of digoxin. So, it's a matter of time and it's a matter of downhill course for the functioning of the kidney.

Q. Well, when digoxin is injected into an individual or gets into the bloodstream, the level rate starts to rise?

A. It's a peak, yes, very quickly if you are given an IV.

Q. And then it starts to fall as the substance is being excreted or metabolized?

A. Well, due to excretion but also due to distribution because when you introduce it into the bloodstream it's going to distribute into tissues and into tissue fluids, et cetera. So, there is a distribution phase and then there is an elimination phase.

Q. And as it distributes into tissue, the level in the blood drops?

A. That's correct.

Q. And the level in the tissue rises?

A. Yes.

Q. All right. And then if there is







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a renal failure, why is there a rise in the level of the blood?

A. Well, once one has dosed the individual and you have them within a given therapeutic window or level at a given therapeutic level, then the major factor that determines the level of blood in digoxin will be, number one, the rate at which the drug is given and, number two, the rate at which it's eliminated.

Now, if you continue to give the drug and you have affected the rate at which it's eliminated, you are going to eventually become toxic. So, in other words, in this individual, they have affected one aspect of the - they have interfered in some way with the rate at which the drug can be eliminated from the system. The thing that's interesting about this particular article is that they discontinued giving digoxin and came back and measured the blood 10 days later and you would expect that at worst that the blood level would have remained the same or at least have gone down a bit or in fact it had gone up quite a bit.

Q. Does that suggest that it came out of the tissues?

A. Certainly that would have to be





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one possibility. But the thing that was interesting about this study was that they measured that one sample with five different methodologies and all five methods gave a different answer, whereas, in their control patient who had normal renal function with being treated with digoxin, the same five kits virtually gave the same answer.

So, something was happening there that maybe it was a digoxin metabolite they were dealing with, maybe they do postulate, it might be a digoxin-like substance. There are about six or seven possibilities that they list to account for their observations.

Q. Doctor, your study which resulted in the letter to the New England Journal was carried out when? I know it was published in the Journal in April, but when were your results actually formulated?

A. Oh, we knew these results probably last September.

Q. And since that time, as we have seen from some of the materials put forward by Mr. Lamek, other people have been studying this same phenomenon, if you can call it that. Have, to your knowledge, any of the manufacturers of these tests been studying this same phenomenon in order to





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determine whether or not what has gone wrong is a result of what's been put into the kits or there's some other reason?

A. Well, I've heard from salesmen and that sort of level of communication that certainly NML and Clinical Assays were assessing the problem and trying to raise an antibody that had a minimum degree of cross-reactivity with this endogenous material.

So, in that sense I guess they're interested in it and pursuing it, but the other interesting observation is that once we identified the antibody law that gave us the highest degree of cross-reactivity, we had verbal commitment from the company for all the remaining stock of that antibody that they had and then in fact when we approached them after the publication of the article to say where is it, there was a lot of humming and hawing and they gave us some of it but not all of it.

MR. MANNING: Probably talked to their lawyers. Thank you very much, Doctor.

THE WITNESS: Thank you.

THE COMMISSIONER: Okay. Mr. Lamek?  
Oh, Mr. Tobias, you're here.

MR. TOBIAS: Yes thank you, Mr.  
Commissioner.







DD 9

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2 CROSS-EXAMINATION BY MR. TOBIAS:

3 Q. Dr. Seccombe, part of the  
4 advantage of cross-examining last is that I can be  
5 very brief because most of my colleagues have  
6 probably asked all the important questions already.

7 In your studies you indicated in chief,  
8 or perhaps in answer to one of Mr. Strathy's questions,  
9 that you had not attempted to refine your sample for  
10 this particular study, and I am referring now to the  
11 study that resulted in the letter to the New England  
12 Journal of Medicine, that you had not attempted to  
13 refine your samples using the high pressure liquid  
chromotography method.

14 You are obviously familiar with that  
15 technique. Are you aware of any other techniques  
16 other than HPLC that would assist one in refining the  
17 sample to try and eliminate what we've been referring  
to as substance X, or other digoxin-like drugs?

18 A. Well, I guess that there  
19 probably could be a series of methodologies that one  
20 could use to try and purify and isolate this material  
21 and separate from digoxin. I think probably the most  
22 powerful and fastest method you have available is the  
23 high pressure liquid chromatography. I mean, that's  
24 the one that we are certainly gearing up to do.  
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The other thing though that I would want to do would be look at differential rates of extraction out of tissue using different solvent systems because we are finding that our substance X will extract out of the tissue at a different level of efficiency than does digoxin, depending on which particular extraction and solvent system you're using.

You could get into column chromatography, affinity chromatography and some of these other methodologies that are used for purification processes.

We felt that high pressure liquid chromatography, certainly from studying digoxin itself and also trying to identify and purify our material it would be the fastest route to go.

So, we are gearing up to do it that way.

Q. So, it is presently your intention in your further studies to subject your test results to the HPLC method?

A. Certainly. I think you'll find that we'll use high pressure liquid chromatography for purification purposes initially.

Q. All right. Is it fair to say then, and I don't want to put words in your mouth, but is it fair to say that because that is the method that you intend to use first and foremost, that in your





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opinion that is most effective means of purifying the sample of all the means that are available to you under which you have knowledge?

A. It is the most expedient way I would say and I haven't had enough experience with the others yet with our substance to really make a judgment as to whether high pressure liquid chromatography in fact is the route to go with it, but certainly, given the background knowledge we have, I would say that it certainly has to be your number one priority.

Q. All right, that's fair. Now, am I correct in my understanding that both HPLC and these other methodologies that we've been talking about, that what we are really trying to do is eliminate the presence in that sample of other digoxin-like substances?

A. In a nutshell that's what you're attempting to do, separate them at least to such an extent that you can eliminate the contaminating factor which is the X.

Q. All right. And in your opinion in any event, HPLC would be the very first test to run, first thing to do in trying to eliminate those substances?

A. Yes, that's the one we selected





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to follow.

Q. All right. Now, in the study that we've been talking about this morning, I think you said at one point that you had had an opportunity to study the interaction of the substance which you have identified as Substance X with other drugs, and that was one of the variables that you took into account?

A. I said that basically we were unable in that initial 25 samplings to see any correlation with drugs, whether the baby was receiving any drug and the level. We looked at all the possible parameters that we could, given the data we had, to see if there was some correlation there. It was a very small sample size and I think that that probably limited the effectiveness of our statistics.

Q. All right. But within those parameters, and given that qualification, you obviously must have been satisfied that there was no correlation, no effect of these other drugs that the babies had been administered?

A. That's right.

Q. In their readings?

A. That's right.

Q. All right. Now, can I take it







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that some of the drugs that you were looking at were gentamicin and ampicillin?

A. Well, I'd have to go back to look at the - certainly if it is listed in there.

Q. I believe the letter to the New England Journal of Medicine contains a chart. May I, Mr. Lamek, please?

A. Yes, there's a gentamicin and tobramycin there as well.

Q. Yes.

A. Well, there's a gentamicin anyway. I don't see tobramycin but then maybe some of the other infants as well were on - I just can't remember the rest of the population. We've got 10 here, there are 15 others, some of which probably in all likelihood were on antibiotics.

Q. All right. Now, can you assist me, gentamicin in particular, or sorry, ampicillin, is that within the penicillin family?

A. Yes.

Q. And would that be a drug normally or routinely used in the treatment of pneumonia?

A. It often is.

Q. All right. And gentamicin, is that also an antibiotic?





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A. Yes.

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Q. Does that come from generally

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the same family as ampicillin or are there basic

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differences between the two drugs?

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A. I think it is a different family but I am not a pharmacologist but it is an antibiotic that is frequently used.

Q. And in particular, referring you to Table 1 to your article, with respect to patient No. 5, when I look under the column "Medication", I see that two drugs that that patient had been administered were gentamicin and ampicillin. From the lack of reference to any other drug for patient No. 5, can I therefore safely assume that with respect to that patient the only other drug that you were aware of that he was administered, that she was administered was gentamicin and ampicillin.

A. That is the documented drugs, yes.

Q. Now we heard last week I suppose from Mr. Cimbura, that with respect to the readings obtained by the RIA technique and as refined by the HPLC technique, we would expect to find some variance relating to a number of variables. The variables that he referred us to where the site the blood sample was drawn from, and the amount of drug that was administered and the time of administration. With respect to your particular study and your findings of the detection of this





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2 substance X, what controls did you use with respect  
3 to those variables? In other words, with respect  
4 in particular to the site from which the blood  
5 sample was taken.

6 MR. LAMEK: Mr. Commissioner, before  
7 we go on I know Mr. Tobias doesn't mean to misstate  
8 the evidence but I don't recall any suggestion from  
9 Mr. Cimbura that the ante mortem blood test turned  
10 in any way upon the site from which the blood was  
11 drawn, and I don't recall that, and the evidence  
yesterday was to the same effect as I recall it.

12 MR. TOBIAS: All right. I think  
13 that is a fair comment and I may very well have mis-  
14 read my own notes and my own recollection of the  
15 evidence. Let me ask the question directly.

16 THE COMMISSIONER: Before you ask  
17 the question, Mr. Tobias, the second variable you  
18 said had something to do with the time of administra-  
tion.

19 MR. TOBIAS: Yes.

20 THE COMMISSIONER: Whereas as I  
21 understood it in all of these cases were  
22 ones where there was no digoxin administered.

23 MR. TOBIAS: That is correct.

24 THE COMMISSIONER: I wouldn't have  
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thought the second had any effect.

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MR. TOBIAS: The second and third variable, Mr. Commissioner, would not be appropriate to this particular test because of the fact there was no administration of digoxin, so therefore we couldn't have an amount of dosage of digoxin or a time.

Q. Let me ask another question with respect to the site that the blood sample is taken from directly. With respect to ante mortem levels, would you expect there to be, can you confirm for us what we thought the evidence of Mr. Cimbura was to the effect that with respect to ante mortem blood samples the site that the sample was taken from would be irrelevant?

A. Well that is the - that is what we have assumed. I am not aware, certainly when one is drawing blood samples one assumes - it can be a problem depending on where you draw it from. Particularly with these kiddies you are either doing a scalp sample, or you have an IV line and you are drawing your blood from those two spots. The degree: I don't think, at least in our work anyway, we assumed that the site of sampling was not of importance for our substance.





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Q. That in effect was specifically  
my next question.

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A. Yes.

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Q. With respect to this phenomenon  
specifically as it relates to what we have been  
calling substance X, you would not be concerned  
therefore with what site the blood sample was drawn  
from.

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A. Given our state of knowledge  
at the moment we wouldn't be.

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MR. TOBIAS: Thank you, those are  
all my questions.

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THE COMMISSIONER: Mr. Lamek, are  
you re-examining?

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MR. LAMEK: Very briefly if I may.

THE COMMISSIONER: You don't want  
time?

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MR. LAMEK: No, I don't think so,  
thank you.

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RE-EXAMINATION BY MR. LAMEK:

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Q. Dr. Seccombe, in response to  
a question from Mr. Strathy and in particular in  
relation to such analyses as you have carried out  
on post mortem tissues, without speaking of  
particular levels recorded, you did say that some





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levels had been so low as to be called non-existent?

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A. That is correct.

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Q. And others you said were well  
into the significant level.

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A. Correct.

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Q. Now, we know that with respect  
to serum you regard anything in excess of .2 nanograms  
as a significant level, is that fair?

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A. Correct.

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Q. What is the level which you  
regard as the threshold of significance in tissue?

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A. I would say anything less than  
.2 we basically are using the same cut-off point.

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Q. .2 nanograms per gram?

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A. Yes.

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THE COMMISSIONER: Did we not hear  
some evidence that in tissue the levels are vastly  
greater, did we not hear that? I am asking you,  
Mr. Lamek?

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MR. LAMEK: Yes, I am sorry, we did indeed  
and I shall be glad to have the Doctor's comment on  
it.

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Q. We have heard, Doctor, and I  
ask you if it is your understanding that once study  
state has been achieved with this drug one might







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2 expect to find concentrations in tissue and in  
3 particular heart, liver and kidney, which in terms  
4 of numbers of nanograms are substantially greater than  
5 you would expect to find in serum?

6 A. That is right.

7 Q. Is that your understanding too?

8 A. Yes.

9 Q. Can you tell me then why you  
10 consider it appropriate to take the same threshold  
level of significance in tissue as in blood?

11 A. Well, basically we are talking  
12 about our substance X as opposed to digoxin. We  
13 would extract a certain amount of tissue and it  
14 really came down to the sensitivity of our methodology  
15 and .2 is absolutely nothing, but depending on where  
16 we look we can get higher levels than that, but  
17 tissue levels of digoxin there is no doubt is very  
much higher.

18 Q. Do I understand that what I am  
19 calling your threshold level of significance ---

20 A. Yes.

21 Q. For your purposes is a positive  
22 reading?

23 A. Yes, a positive reading that  
24 would represent above the lower limit of sensitivity  
25 for the assay methodology we have been using, yes.





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Q. And they have nothing to do with activity, levels of activity, therapeutic, toxic or anything else?

A. Oh, no.

Q. A detectable positive ---

A. That's right, we are investigating and we don't know what we are going to find. So we'd like to kind of measure the minimum amount that we possibly can measure and say, well, that's low and that's high, you know it is all a relative situation.

Q. I did want to be clear.

A. Yes.

Q. It is important, because it is a thought that has occurred to me I confess frequently during your cross-examination particularly, that in a sense although what you are doing is clearly of interest to this Commission, your interests and ours are very different, are they not? In this sense that your prime interest is to isolate and identify substance X?

A. That is true.

Q. Our prime interest in sampling techniques is how best to isolate and identify digoxin, isn't it?





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A. That is right.

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Q. And those are not necessarily  
two sides of the same coin, are they?

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A. Only in respect to how much  
does our - the presence of our X influence your  
levels.

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Q. That's right.

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A. That's right.  
Q. But ideally if you could  
isolate substance X by RIA, HPLC in combination  
or separately, or by any other way, you wouldn't  
care what else was there for your present purposes,  
would you?

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A. No.

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Q. And equally if there were a  
technique that were capable of identifying digoxin  
and only digoxin, and I suppose people interested  
in achieving that wouldn't care what else was there,  
would they?

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A. That's true.

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Q. So we are approaching these  
things from two rather different viewpoints, are  
we not?

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A. For sure, yes.

Q. And that is why the antibody







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2 which you find most attractive for your purposes is  
3 the very one that for digoxin assays is the  
4 least attractive, isn't it?

5 A. That is true.

6 Q. Because your NML first batch,  
7 or first lot antibody is the one that picks up most  
8 of the substance that you are interested in and  
9 it is that very feature of it which makes it least  
10 desirable for digoxin assay, isn't it?

11 A. That is true.

12 Q. I think the thing that you  
13 said that drew that most clearly to my attention,  
14 was when Mr. Olah was asking you about the possi-  
15 bility of this multiplier effect occurring in  
16 post mortem serum as opposed to ante mortem serum  
17 with respect to substance X. You said, well, you  
18 recounted an investigation you had done in such  
19 samples from a child who had been receiving digoxin,  
20 and you said that study was contaminated with  
21 digoxin?

22 A. That's right.

23 Q. Now, from your point of view  
24 that is a perfectly proper observation, is it not?

25 A. I felt it was.

Q. The digoxin was getting in your  
way?







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A. That is for sure.

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Q. From where we are sitting it may be that your substance X and other things are getting in our way?

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A. That is correct.

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Q. Two other small points if I may. In the course of Mr. Strathy's cross-examination you referred to a child I think with the level of 5.4 or 6, I think it was a hypothetical child or an actual child I don't know. You were trying to illustrate I believe, you were illustrating, the obscuring effect that could result from the presence of substance X. You suggested a level in a child of 5.4 or 6 nanograms per millilitre which you said would appear grossly toxic. I was particularly struck by those words and I made a note of them. Do I take it from that that a level of 5.4 to 6 nanograms per millilitre in ante mortem serum would prima facie be a level which you would regard as indicative of gross toxicity?

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A. Regarding that particular case all I know is that I received the phone call from the physician that was treating that infant and there was considerable concern about the toxic levels of the drug. He would be in a better





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2 position to establish what is grossly toxic, and  
3 maybe the modifier was a little extreme. Definitely  
4 he was considerably concerned regarding the blood  
5 level and was rather irate that the level in the  
6 span of two days should multiply by twofold and  
7 yet the dosage had remained constant and there had  
8 been no change in renal function.

9 Q. Do I take it, at least from  
10 that, that a level of 5.4, 6 nanograms per millilitre  
11 in the blood of a live child is one which would cause  
12 prima facie concern about toxicity?

13 A. It certainly did in this  
14 particular case.

15 Q. Now, it may be that there is  
16 some distortion of the result by the presence of  
17 your substance, or other things which are attracted  
18 on the RIA without any separation of the sample, but  
19 on its face that is a level, in your judgment is it,  
20 that gives rise to questions of toxicity?

21 A. With the limited experience I  
22 have had dealing with clinicians, yes.

23 Q. One other matter and it goes  
24 to the question of the high pressure liquid  
25 chromatography. You were asked as to the likelihood  
that HPLC will indeed separate out your substance X





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from a serum sample. Your answer as I understood it was that would depend upon how structurally similar substance X is to digoxin. You assumed a close similarity because it is capable of binding with the antibody for digoxin, is that fair?

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A. Yes.

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Q. Is there any reason, Doctor, to believe though, or to think that substance X may be any more structurally similar to digoxin than any of those digoxin metabolites which we also know bind to the antibody but which are separable by HPLC?

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A. I think that is an open question and that is very much a real concern of mine.

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Q. The mere capacity of this substance to bind with the antibody is in itself no necessary indication that it is so structurally similar that it would come out of the HPLC column in the same peak as digoxin itself?

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A. That is true.

MR. LAMEK: Thank you very much, Doctor, you have been very helpful.

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THE WITNESS: You are welcome.

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MR. STRATHY: Just before we release Dr. Seccombe to the west coast, there is one matter that is of some concern to me.

I do not in any way want to put Dr. Seccombe in jeopardy with the publishers of his upcoming article but obviously, as Mr. Lamek has said, if you are on the cutting edge as it were of the research it would be desirable at some point, and obviously the sooner the better, to have access to that article.

THE COMMISSIONER: Which article are we referring to?

MR. STRATHY: It is the latest one, I gather, that has been submitted to the publisher of the journal, and is being reviewed.

THE COMMISSIONER: Is that the one that was to be delivered in Quebec?

MR. STRATHY: No, I gather it is a further one. It has been prepared and submitted and it may be eight to twelve weeks before it is published.

THE COMMISSIONER: All right.

THE WITNESS: That is correct.

MR. STRATHY: I may be making a lot more out of it than there is, in fact, but it would certainly be helpful to have a look at it.





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MR. LAMEK: Mr. Commissioner, Mr.

Strathy did speak to me about this at lunch and he very properly understands Dr. Seccombe's reluctance to make any kind of publication of a paper which has been submitted for publication because that might impair its acceptability by the journal to which it is being submitted. Mr. Strathy understands that, and he is not in any way interested in embarrassing Dr. Seccombe in that way.

I think we will have to ask Dr..

Seccombe at what point in the publication process this paper, which has been submitted, may properly be distributed to people here. That is the first question. Then, whether Dr. Seccombe may be available for further evidence with respect to that paper. He is not being questioned too closely about it because there is no wish to make pre-publication, if you will, of the matters contained in it.

MR. STRATHY: Yes indeed, Mr.

Commissioner, and if I may, a further step once removed from that, even if we might have access to it with respect to reading a copy of it, without it being reproduced.

MR. LAMEK: I think we have to be





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guided to a very large extent by Dr. Seccombe on that, and he should recognize --

THE COMMISSIONER: What do you say about all of this, Dr. Seccombe.

THE WITNESS: Well I guess the difficulty has obviously been expressed and it really comes down to the editorial policies of the journal that it has been submitted to, and I am in no position at the moment to elucidate what those are. Some journals are very strict as to that sort of thing; others tend to be a little more openminded. I would be happy to look into it when I get back to Vancouver.

THE COMMISSIONER: You say the publication will be when?

THE WITNESS: This is a variable that one has no control over, but typically you are looking at eight to twelve weeks for the review process and then there is a delay, after acceptance, prior to it being published which may amount to a matter of months or years or weeks.

THE COMMISSIONER: Can we follow it up to see whether the journal will -- if I can be of assistance I will certainly sign anything that is put before me -- within reason.







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MR. LAMEK: Dr. Seccombe, if the paper is accepted for publication, and I am confident it will be, perhaps upon its acceptance you could let us know if you may then --

THE WITNESS: I will contact the editor of the journal when I get back to Vancouver and explain the situation and see what his particular bias is.

MR. LAMEK: And if you could persuade him to expedite that review period as well, that too would be helpful.

THE COMMISSIONER: In the most unlikely event that it is refused then I suppose it is yours to --

THE WITNESS: It is up for grabs, and it will probably be rewritten and revised and resubmitted.

MR. LAMEK: We are not deterred by one rejection slip, Mr. Commissioner.

THE COMMISSIONER: All right. Well I think we know where we are at. Does that solve your problem -- at least, it does not solve your problem but it the best --

MR. STRATHY: It is a practical solution.







FF-5

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MR. LAMEK: Thank you very much.

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THE COMMISSIONER: Thank you very

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much, Doctor, indeed.

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MR. LAMEK: We have gone a little

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longer with Dr. Seccombe than we thought at lunchtime

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that we might. I wonder if I might suggest this.

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Rather than starting with Dr. Ellis tonight, and

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I have no authorization from counsel for the Hospital

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to suggest this, but I wonder if it might be useful

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if his counsel is prepared to have it.

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THE COMMISSIONER: What do you say,

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Mr. Roland?

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MR. ROLAND: I think I can accept on

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behalf of Dr. Ellis. He has been here all day waiting

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to be called and I think, for another half hour, he

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would be prepared to meet with Counsel.

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MR. LAMEK: If that were so, we could

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start fresh with him in the morning.

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THE COMMISSIONER: All right. That

is what we will do, and at this moment --

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MR. ORTVED: May I say something,

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Mr. Commissioner?

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THE COMMISSIONER: Yes, all right.

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MR. ORTVED: Mr. Commissioner, I want

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to renew at this time my application for the Atlanta Report and the reason is this: Mr. Lamek has advised me that following upon the evidence concerning the testing for digoxin it is his present intention to then commence hearing from certain of the doctors of the Division of Cardiology. He has indicated to me further that his present plan is to call those doctors, really for all purposes, which would include the chronology, going back to July, 1980 and really continuing up to the present time.

Part of what he will obviously canvass with them is not only their respective reviews of the deaths during the period 1980 - 1981, but we can imagine their retrospective reviews of all of those deaths.

It strikes me that, firstly, we have here terms of reference which detail you to inquire into certain reports, one of which is the Atlanta Report, in which we know from the abstracts characterizes certain of those deaths differently than others, and it is my submission to you that those doctors, Dr. Rowe in particular, might be of assistance to you in terms of his views of those deaths having regard to what is said about them by Atlanta.





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Secondly, we are in the situation of Dr. Rowe as a witness asked in all likelihood to comment on certain of the deaths when there are counsel here who are in possession of information with which to cross-examine Dr. Rowe, as contained in the Atlanta Report, and to which he is not privy. That strikes me as unfair.

So, for two reasons, I renew my request to you, firstly on the basis of assisting you to arrive at the bottom of this in the very best manner you can, and, secondly, on the basis of fairness. If Dr. Rowe is to be called, then he should have access to the Atlanta Report first.

THE COMMISSIONER: Thank you, Mr. Ortved. You know of course that there is a delicate balance that we have to --

MR. ORTVED: I am aware of that.

THE COMMISSIONER: It would certainly assist you and for that purpose I am concerned about your ability to cross-examine with one of the documents being withheld; the other problem of course is if it is released prematurely there is a problem as to an injustice being done vastly, perhaps vastly more serious. I do not know; that is the problem, I am not deciding anything. We are going to discuss







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this further with you and perhaps with other counsel.

What I would like to happen is that immediately we rise and before anybody attacks Dr. Ellis, the next witness, I would like to see in my chambers those counsel to whom I delivered a copy of the Atlanta Report and see if we cannot perhaps solve your problem. That does not include you, obviously, Mr. Ortved, but perhaps we may be able to solve that problem.

MR. ORTVED: All right.

THE COMMISSIONER: Yes, Mr. Manning.

MR. MANNING: I would like to endorse those comments.

THE COMMISSIONER: I thought you would.

MR. MANNING: I am not repeating it. I do have a problem with respect to timing. I am sure that that is also the problem of most counsel.

Mr. Orved has obviously, through his contact with Mr. Lamek, received some information as to what Mr. Lamek hopes will develop in the next little while and the order in which he hopes to proceed. Having been in the position of having to call witnesses out of order for many years. I fully appreciate counsel's problem. I wonder if Mr.





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Lamek can be in a position in the next few days to give all counsel an outline of where they expect to be going with respect to the kind of witnesses and who they expect to be calling.

THE COMMISSIONER: I suppose if you don't hold it against them when it turns out that they can't follow it.

MR. MANNING: Of course not. We all appreciate, Mr. Commissioner, the difficulty of trying to time witness.

MR. LAMEK: Mr. Commissioner, let there be no misunderstanding about this. I have advised all counsel to the best of my ability as soon as possible as to the sequence of witnesses. It was only when to my surprise today -- it looked at lunchtime as though we were going to be through with Dr. Seccombe by the middle of the afternoon -- but it occurred to me that next week, which I had otherwise thought to be filled with witnesses was going to have to be reorganized.

The reason that I spoke to Mr. Ortved and indeed to Miss Devins about calling the doctors is that it is their clients that I need to talk to in a hurry to find out their availability. No preferential information has been given out,





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let me put Mr. Manning's mind at ease ---

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MR. MANNING: I was not suggesting

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that.

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MR. LAMEK: He will know as soon

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as a plan is arranged.

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MR. MANNING: I was not suggesting

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that.

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THE COMMISSIONER: All right, I

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think the schedule that we have been given so far,

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I found very helpful, and I am trusting that you

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and having that vote of confidence I think Mr. Lamek

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and Miss Cronk will continue that and will perhaps

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expand it to take in a bit more, if you can.

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MR. LAMEK: If possible.

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THE COMMISSIONER: We will rise.

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I want to see those counsel that I indicated in

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my chambers right now and the rest -- what time and

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where will Dr. Ellis be, do we know?

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MR. LAMEK: Mr. Commissioner, we

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were just considering that very question. We met

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at lunchtime in the jury room which Miss Cronk

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and I are using as counsel room, and if that is

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convenient to the court we might as well meet there.

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THE COMMISSIONER: All right, then,







FF-11

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Mr. Roland.

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MR. ROLAND: Yes.

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THE COMMISSIONER: Can you save it  
for five minutes or ten minutes or something like  
that before it starts?

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MR. LAMEK: Sure.

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THE COMMISSIONER: All right, until  
10:00 o'clock tomorrow morning.

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---Whereupon the hearing adjourned at 4:00 p.m.  
until Wednesday, June 29th, 1983 at 10:00 a.m.

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